DOCTOR OF MEDICINE

An Investigation into the Efficacy of Interventional Therapy for Oral Potentially Malignant Disorders. Population Studies from North-East England

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An Investigation into the Efficacy of Interventional Therapy for Oral Potentially Malignant Disorders

Population Studies from North-East England

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A thesis submitted for the Degree of Doctor of Medicine

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DOCTOR OF MEDICINE

CANDIDATE DECLARATION

Peter James Thomson

Department for Health

1. This thesis embodies the results of personal clinical academic work I have carried out in the field of oral potentially malignant disorder diagnosis and management whilst employed as Professor of Oral & Maxillofacial Surgery at Newcastle University and during my clinical practice as an honorary consultant maxillofacial surgeon at the Newcastle upon Tyne Hospitals NHS Foundation Trust between 1996 and 2015.

2. The thesis also includes a body of pertinent published and presented works embodying the results of personal observations and research within this field. In these papers, where there are multiple authors, I am either the first-named or principal author having initiated both the academic enquiry and personally undertaken or directed the clinical research work.

3. Whilst the intellectual content for the academic work presented for this Doctorate of Medicine has not been submitted in this format for support of a successful or pending application for any other degree or qualification of this or any other University or of any professional or learned body:

(a) A number of published clinical studies have partially utilised clinical and pathological data from patients treated by the author; these studies are fully referenced in the thesis, and

(b) Clinical and pathological data from the author's treated patients have also been utilised and contributed in part to the following higher degrees -

R A Green. *Patient and Professional Views and Experience of Oral Precancer.* PhD Thesis. Newcastle University (2013)

M L Goodson. '*Objective Diagnosis' and the Clinical Outcome of Oral Potentially Malignant Disorders.* PhD Thesis. Newcastle University (2014)

I confirm that this is a true statement and that, subject to any comments above, the submission is my own original work.

Signed: **Date:** 1 March 2016

ABSTRACT

Oral squamous cell carcinoma (SCC) is a lethal, deforming disease of global significance and rising incidence. In 2011, 6,767 new cases and 2,056 deaths occurred in the UK. Cancers are preceded by oral potentially malignant disorders (PMD), recognizable mucosal diseases harbouring significantly increased risk of carcinoma. These manifestations offer clinicians a 'therapeutic window' to intervene during carcinogenesis, although contemporary practice remains unable to predict individual lesion behaviour or quantify risk for malignant transformation. No clear management guidelines exist and available scientific literature is unable to answer the fundamental question whether intervention prevents cancer.

This MD thesis includes 7 published papers on oral pre-cancer and 4 observational studies from a specialist PMD service coordinated by the author in Newcastle upon Tyne in Northern England.

PMD management involves a complex interaction between patients, clinicians' views on diagnosis and treatment and histopathological assessment of mucosal biopsy specimens. Uncertainty regarding the 'potentially malignant state' remains a pernicious influence throughout.

Newcastle PMD patients were profiled as predominantly male, with a median age of 60yrs, and regular users of both tobacco and alcohol. Most presented with single-site disease, primarily leukoplakia on the floor of mouth and ventro-lateral tongue, with over 80% exhibiting epithelial dysplasia on histopathological examination. Approximately 70% underwent interventional therapy using CO_2 laser surgery.

840 laser treatments were performed between 1996 and 2015 and the efficacy of laser intervention was examined by reviewing clinico-pathological details and clinical outcome for 590 PMD patients followed for a mean of 7.3yrs. Histopathology required 'up-grading' in 36% following definitive examination of laser excision specimens. 74.2% of patients were disease free, primarily younger patients with 'low-grade' dysplasia, 9% exhibited persistent disease and were older with gingival lesions often proliferative verrucous leukoplakia (PVL). In 12%, unexpected SCC was identified on excision, whilst 4.8% transformed to malignancy.

Interventional laser surgery facilitates definitive diagnosis and efficacious treatment, allows early diagnosis and treatment of SCC, identifies patients at risk of progressive disease and defines clinical outcome categories. Evidence is lacking, however, that intervention halts the progress of carcinogenesis.

Multi-centre, prospective, randomized, controlled trials are needed to confirm the efficacy of interventional surgery, to characterise PMD natural history and to disseminate research findings. It is hoped that the clinical work presented in this MD thesis will inform and encourage further research into PMD and lead to a reduction in the incidence of malignancy and improved morbidity and mortality.

Chapter One

INTRODUCTION

1.1 Oral Squamous Cell Carcinoma

Oral cancer, principally squamous cell carcinoma (SCC) arising from the mucosal lining of the mouth, presents clinically as non-healing erosive or ulcerative lesions which progress to irregular, raised, invasive and ultimately painful tumour growths. Established oral carcinoma, which is one of the commonest head and neck malignancies, is a lethal and deforming disease due to local invasion, oral and facial destruction, metastasis to cervical lymph nodes and widespread blood-borne tumour dissemination particularly affecting the lungs and the liver (Mehanna et al 2010a & 2010b). The clinical severity of the disease, and its significant systemic nature, is well-illustrated in Figure 1.1.

Worldwide, oral cancer is estimated to be the 6th most common cancer with 5-year survival rates around 50% and a prognosis significantly compromised by advanced disease and late presentation, which are common features in contemporary clinical practice (Conway et al 2008, Warnakulasuriya 2009). In the UK 6,767 new cases of oral cancer were diagnosed in 2011, with 2,056 deaths reported (National Cancer Intelligence Network 2014). There has been a significant rise in incidence, particularly affecting young and female patients, and researchers predict an 'epidemic' of mouth cancer will occur during the 21st Century (Warnakulasuriya 2009 & 2010, Kalavrezos & Bhandari 2010).

Whilst the number of patients suffering uncontrolled oral cancer disease at primary sites in the head and neck has fallen over the last 30 years, due to improved management techniques, primarily combining treatment modalities of surgery and chemo-radiotherapy, many will die as a result of metastatic disease and up to a quarter of patients experience multiple cancer development in the upper aerodigestive tract either synchronously or metachronously (Mehanna et al 2010b, Shah & Gil 2009).

Figure 1.1: Oral Squamous Cell Carcinoma showing (A) invasive, ulcerated lesion arising on the posterior tongue and retromolar region with associated leukoplakia of the faucial pillars, (B) CT scan confirming metastatic tumour deposits affecting both submandibular and upper deep cervical lymph nodes, and (C) chest radiography illustrating extensive pulmonary metastatic disease.

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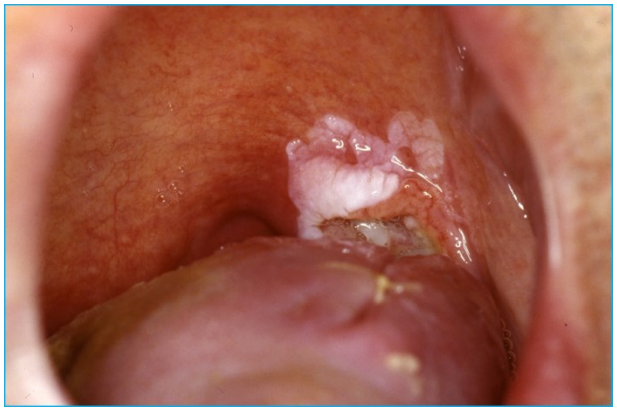

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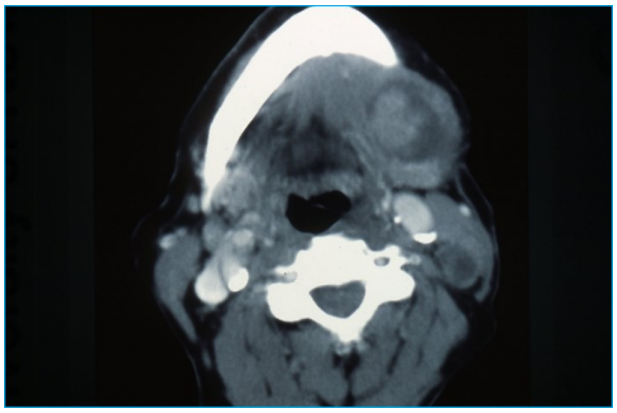

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The presentation of multiple lesions in an individual patient is a manifestation of widespread epithelial instability, which is a hallmark of head and neck squamous cell carcinoma, classically referred to as 'field change' cancerization (Dakubo et al 2007). This was the term first introduced by Slaughter et al (1953) who proposed that oral cancers develop in multifocal areas of 'pre-cancer change'. The risk of multiple, primary cancer development is probably highest in younger patients and those continually exposed to carcinogenic influence (Warnakulasuriya 2009, Hamadah et al 2010).

Aetiological factors responsible for malignant transformation of oral squamous epithelium most commonly involve the excessive consumption of tobacco products and alcohol misuse (Anantharaman et al 2011, Lee et al 2013). Globally, 25% of oral cancers have been attributed to tobacco use, either by smoking or chewing habits, and an association that is dose-dependent increasing markedly for smoking durations greater than 20 years, daily cigarette consumption in excess of 20 and enhanced addiction to tobacco (Petti 2009, Lee et al 2013).

Around 7 to 19% of oral cancer cases have been linked with regular alcohol consumption which also seems to increase risk in a dose-dependent manner, such that individuals consuming 4 to 5 drinks daily show a 2 to 3 times higher risk than non-drinkers (Marron et al 2012). Whilst there is no doubt that oral cancer risk increases further amongst alcohol drinkers who also smoke, uncertainty remains regarding the true significance of alcohol use in people who have never smoked (Petti 2009, Hashibe et al 2007).

A further complication is that many people who smoke and drink do not develop cancer whilst other studies have observed that, equally, many oral cancer patients have never been overexposed to tobacco or alcohol, so it is likely that other risk factors are involved (Macfarlane et al 2010). Genetic predisposition to DNA mutation in oral epithelium, poor diet and nutrition, ageing, an impaired immune response, low socioeconomic status, short stature, manual occupations, poor oral health and infections have all been implicated, but evidence of their precise role in carcinogenesis remains

obtuse and is still evolving (Zain 2001, Conway et al 2008 & 2010, Lagiou et al 2009a & 2009b, Donadini et al 2010, Johnson et al 2010, Warnakulasuriya 2010, Edefonti et al 2011, Chuang et al 2012, Ahrens 2014, Leoncini et al 2014). Petti (2009), for example, reported that 10 to 15% of oral cancer cases may be attributed to diets low in fresh fruit and vegetable intake, but again the specific interaction between putative anti-carcinogenic properties of the diet versus heavy smoking and alcohol drinking remains unclear.

daSilva et al (2011) also emphasized the close interrelationships that exist between the principal aetiological agents of oral cancer: lifestyle habits (tobacco exposure and alcohol consumption), dietary factors, occupation, socioeconomic status, exposure to external agents and genetic susceptibility.

Although a significant role for human papillomavirus (HPV) infection (especially subtype 16) has been suggested during oral carcinogenesis, this seems uniquely associated with a rise in oropharyngeal, tonsil and tongue base cancer affecting younger patients and often presenting with extensive cervical lymph node metastases and a postulated sexually transmitted aetiology. Thus, HPV associated head and neck cancer probably represents a distinct disease entity and the role of HPV in classic, tobacco-related intra-oral cancer still remains obscure (Mehanna et al 2010a & b, Syrjanen et al 2011, Anantharaman et al 2013).

1.2 Oral Carcinogenesis and Epithelial Dysplasia

A ‘progression model’ proposed for oral carcinogenesis suggests that, following genetic mutation and irreversible genotypic damage, various phenotypic epithelial tissue disorganisation and dysmaturation changes occur which, if allowed to progress, ultimately lead to invasive carcinoma (Califano et al 1996, Donadini et al 2010, Castagnola et al 2011, Thomson 2012b). Such disorganised features preceding cancer are identifiable at the microscopic level and are collectively described as epithelial dysplasia; these are listed in Table 1.1 (Speight 2007, Sloan 2012), and illustrated in Figure 1.2.

Oral epithelial dysplasia is thus an expression of a tissue maturation and cellular proliferation disorder (Warnakulasuriya 2001), and is an important histopathological entity that delineates morphological changes affecting both individual epithelial cells (which take on a more ‘primitive’ appearance) and the overall integrity of epithelial structure (which loses normal maturation and stratification) in lesions at risk of malignancy. In clinical practice, an assessment of the degree of dysplastic change in tissue is made following incision biopsy and microscopic classification into mild, moderate or severe categories, according to the tissue thickness occupied by the atypical epithelium (Speight 2007, Martorell-Calatayud et al 2009); Figure 1.2. As epithelial proliferative units and oral keratinocyte stem cell activity are postulated to lie within the basal and supra-basal layers, it is not surprising that the initial changes of mild dysplasia are first recognised within the basal third of the oral epithelium, ultimately progressing through the higher epithelial layers as severity increases (Warnakulasuriya 2001, Sloan 2012, Thomson 2012b). Carcinoma-in-Situ (CiS) is regarded as the most severe form of epithelial dysplasia and is characterised by full-thickness cytological and architectural disturbance (Speight 2007).

The more severe the dysplasia, the higher the risk of malignant change, although there is a strong subjective element in dysplasia grading and both biopsy sampling error and change in severity over time may confound the

accuracy of diagnosis (Warnakulasuriya 2001, Speight 2007, Sloan 2012, Balasundaram et al 2013, Rastogi et al 2013, Shirani et al 2014).

TABLE 1.1: HISTOPATHOLOGICAL FEATURES OF DYSPLASIA IN ORAL POTENTIALLY MALIGNANT DISORDERS

CYTOLOGY	TISSUE ARCHITECTURE
Variation in Nuclear Size (Anisonucleosis)	Irregular Epithelial Stratification
Variation in Nuclear Shape (Pleomorphism)	Loss of Polarity of Basal Cells
Variation in Cell Size (Anisocytosis)	Drop-shaped Rete Ridges
Variation in Cell Shape (Pleomorphism)	Increased Number of Mitotic Figures
Increased Nuclear to Cytoplasmic Ratio	Abnormally Superficial Mitoses
Increased Nuclear Size	Premature Keratinisation in Single Cells (Dyskeratosis)
Atypical Mitotic Figures	Keratin Pearls within Rete Ridges
Increased Number & Size of Nucleoli	
Hyperchromasia	

Tilakaratne et al (2011) specifically criticised the subjective nature of contemporary dysplasia grading, raising concerns regarding disease definition and terminology, and noted the lack of agreement between pathologists about the relative importance of individual histological features and the overall lack of reproducibility and poor predictive ability of current grading systems. Interestingly, however, these authors were not able to significantly improve objective diagnostic ability by attempting computational analyses and ranking of histopathological features. Dost et al (2014) have also criticised current dysplasia grading systems siting their imprecision, low reproducibility and lack of inter- and intra-observer agreement during the diagnostic process.

Figure 1.2: Histopathological Features of Oral Potentially Malignant Disorders as observed under light microscopy of haematoxylin & eosin-stained tissue sections demonstrating (A) mild dysplasia, with cellular changes predominant in the basal third of the epithelium x400 (B) moderate, with extension of epithelial disorganisation to the middle third x200 (C) severely dysplastic change spreading to involve more than two-thirds of the epithelium x200 and (D) proliferative verrucous leukoplakia, a recurrent multi-focal lesion, illustrating folds of verrucous hyperplasia and marked lymphocytic infiltration beneath the basement membrane; features of dysplasia are often absent x100.

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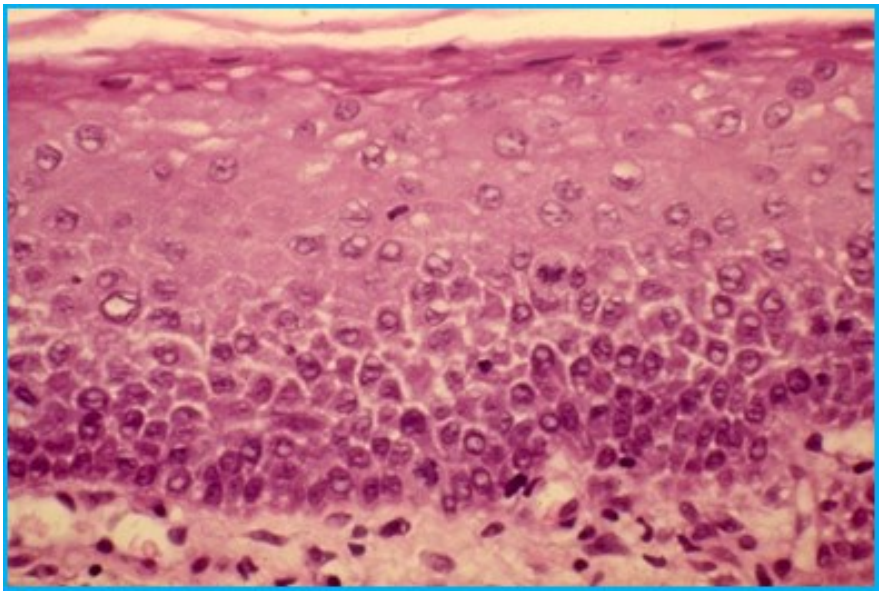

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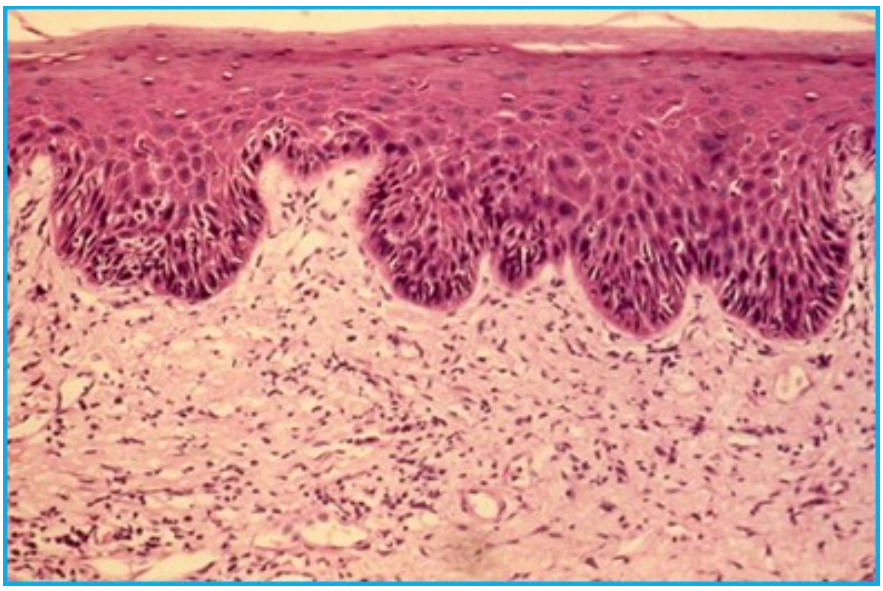

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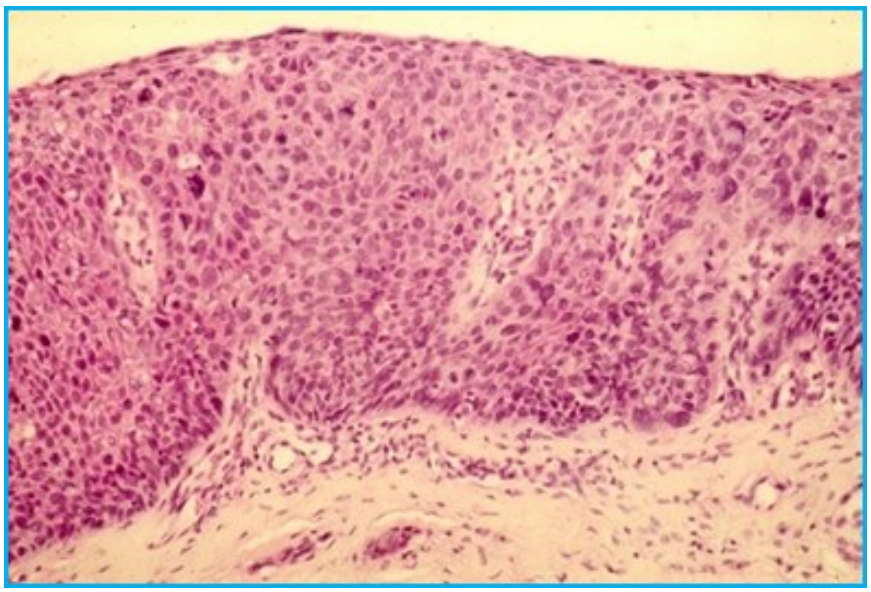

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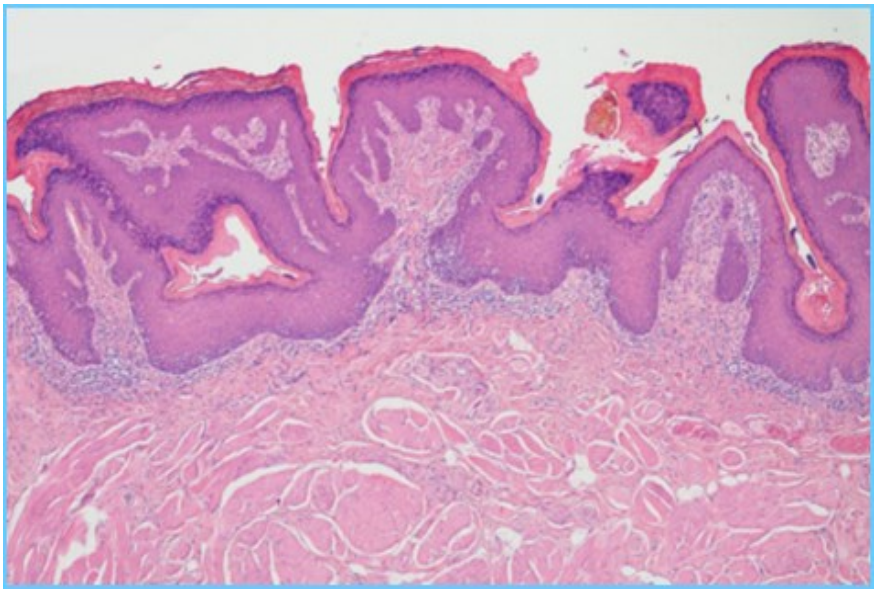

The use of epithelial dysplasia assessment to predict malignant transformation remains problematic because both the overall grading system and the individual features to be characterised are poorly defined (Tilakaratne et al 2011). As a result, a binary dysplasia classification, distinguishing between lesions at 'low' or 'high risk' of cancer progression has been proposed to try to improve objectivity but, despite appealing to clinicians attempting to rationalize treatment intervention, it has not yet found routine application in clinical practice (Kujan et al 2006).

An additional, important observation regarding PMD diagnosis is the realization that even in the absence of epithelial dysplasia some oral mucosal lesions may still transform to cancer (Martorell-Calatayud et al 2009). This has been noted, in particular, for isolated mucosal lesions exhibiting lichenoid inflammatory features (Krutchkoff & Eisenberg 1985, Goodson et al 2010b, Patil et al 2014). In addition early-stage proliferative verrucous leukoplakia, an aggressive multi-focal potentially malignant disorder, with a known high risk of malignancy, shares a number of histopathological features similar to lichenoid mucositis such as hyperkeratosis, sub-epithelial lymphocytic infiltration, basal cell degeneration, and apoptosis, often without the classic features of dysplasia, rendering the diagnostic process complex (Speight 2007, Issrani et al 2013); Figure 1.2D.

Oral epithelial dysplasia, however, remains the 'reference' investigation in oral potentially malignant disorder management and is one of the few clinically applicable predictors of risk for malignant transformation (Reibel 2003, Tilakaratne et al 2011). Similarly, as the association between oral malignancy and the presence of dysplasia remains significant (Schaaij-Visser et al 2010), early intervention to remove pre-cancerous dysplastic tissue appears a logical treatment approach. Dost et al (2014) recently proposed definitive treatment for all oral mucosal lesions exhibiting dysplasia, irrespective of severity. It is indeed this specific concept that forms the basis for the interventional clinical work presented and analysed in this MD thesis.

1.3 Oral Potentially Malignant Disorders

It has been recognized for many years that a spectrum of distinct oral mucosal abnormalities, now termed potentially malignant disorders (PMD) and which accompany dysplastic pre-invasive cancer change, may be identified clinically and characterized, albeit somewhat non-specifically, during oral examination. There is, therefore, an opportunity for both early diagnosis and therapeutic intervention during this clinically identifiable 'oral pre-cancer window' (Thomson 2012a, Mortazavi et al 2014).

Potentially malignant disorders are defined as recognizable oral mucosal diseases which share a significantly increased risk of squamous carcinoma development compared with apparently normal mucosa. The term encompasses both localized lesions and more generalized conditions and, whilst emphasizing that not all will inevitably transform into cancer, also recognizes the widespread, often multi-focal nature of such disease within the entire upper aerodigestive tract (Hamadah et al 2010, Carnelio et al 2011, Thomson 2012b & 2012e).

The list of mucosal diseases considered potentially malignant includes classically described entities such as leukoplakia, erythroplakia, erythroleukoplakia and more recently recognised disorders such as progressive, multi-focal proliferative verrucous leukoplakia (Figure 1.3), as well as widespread conditions such as immunodeficiency, oral submucous fibrosis, chronic hyperplastic candidosis, and perhaps more controversially oral lichenoid lesions (van der Waal 2009a&b, Thomson & Goodson 2012, Yardimci et al 2014, Goodson et al 2010b); Table 1.2.

TABLE 1.2: CLINICAL PRESENTATION OF ORAL POTENTIALLY MALIGNANT DISORDERS	
LOCALIZED ORAL LESIONS	**MORE WIDESPREAD CONDITIONS**
Leukoplakia	Immunosuppression
Erythroplakia	Oral Submucous Fibrosis
Erythroleukoplakia	Lichen Planus and Lichenoid Lesions
Proliferative Verrucous Leukoplakia	Sideropenic Dysphagia
	Discoid Lupus Erythematosus
	Chronic Hyperplastic Candidosis

Estimates of the prevalence of oral potentially malignant disorders suggest an overall figure of between 2 to 3%, with the vast majority appearing clinically as leukoplakias, and usually presenting on the floor of the mouth, ventro-lateral tongue and buccal mucosa. Whilst previously seen as a disorder of older, male patients, increasing evidence suggests that a much younger population is now at risk (Petti 2003, Napier & Speight 2008).

The concept that these disorders represent a recognizable potentially malignant state has arisen following a number of salient clinico-pathological observations including the observed transformation of precursor lesions into invasive cancers during patient follow up, the recognition that leukoplakic or erythroplakic lesions often co-exist with oral squamous cell carcinoma (as seen in Figure 1.1A) and the realization that numerous histopathological and biomolecular tissue changes are common to both cancers and their potentially malignant counterparts (Warnakulasuriya et al 2007).

Figure 1.3: Clinical Appearance of Oral Potentially Malignant Disorders illustrating (A) leukoplakia, the most common clinical presentation, arising on the ventral tongue and floor of mouth, (B) erythroplakia of the anterior floor of mouth, which is a rarer lesion but statistically more likely to exhibit invasive carcinoma, (C) erythroleukoplakia, often referred to as 'speckled leukoplakia', distributed in this example unilaterally on the floor of the mouth and (D) proliferative verrucous leucoplakia, a progressive, multi-focal, fissured and exophytic lesion commonly seen on the gingiva and alveolar mucosa and with a high malignant transformation risk.

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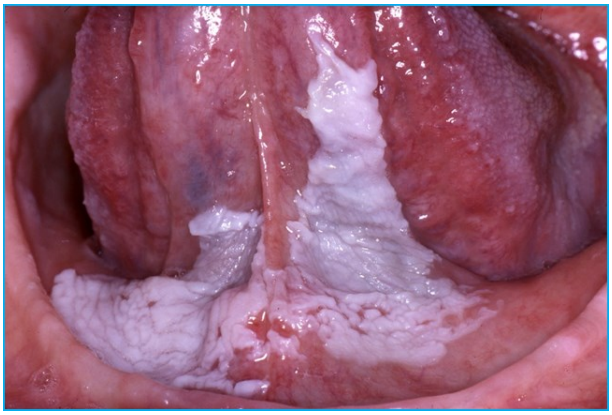

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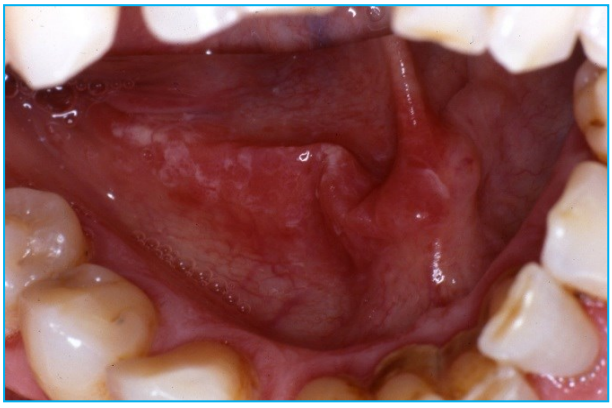

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The identification of a potentially malignant disorder in an individual patient does not mean, however, that inevitable malignant transformation will take place. Many oral lesions do not progress over time, whilst others may resolve or regress spontaneously and it remains impossible in clinical practice to reliably predict the behaviour of any individual lesion or patient. Nonetheless, affected patients remain at increased risk of squamous carcinoma development (Warnakulasuriya 2009).

Attempts have been made to stratify ‘high’ and ‘low’ risk factors for potentially malignant disease development (Diajil et al 2010), but the ability to quantify risk for individual patients remains frustratingly elusive in contemporary practice. By synthesizing data from a number of publications summarizing risk factor research, however, a ‘high risk’ profile for oral carcinogenesis may be postulated: such patients are likely to misuse tobacco and alcohol (Hamadah et al 2007, Macfarlane et al 2010, Anantharaman et al 2011), exhibiting a strong addiction to smoking (Lee et al 2013) and persistent high alcohol consumption (Goodson et al 2010, Marron et al 2012), together with a diet low in fruit and vegetables (Hamadah et al 2010, Chuang et al 2012), and with poor oral hygiene and irregular dental care (Ahrens et al 2014). Most commonly, the patient will be a male of shorter-stature, low socioeconomic status and low educational attainment (Leoncini et al 2014, Conway et al 2014), experiencing periods of material deprivation or long-term unemployment (Greenwood et al 2003) or primarily engaged in manual

occupations such as bricklaying and painting (Richiardi et al 2012). In contrast, patients' age (Macfarlane et al 2010), general medical status (Macfarlane et al 2012) and human papillomavirus exposure (Anantharaman et al 2013) have all been shown to be less helpful in predicting disease status and risk.

1.4 Screening, Prevention and Intervention

In order to improve patient survival and reduce the morbidity following oral cancer diagnosis, it seems logical for oral clinicians to utilize the 'oral pre-cancer window' to identify potentially malignant change at the earliest possible stage and to intervene to halt the disease process (Thomson 2012f). In addition to the professional uncertainties surrounding diagnosis and management of potentially malignant disease there is also, unfortunately, considerable public ignorance regarding oral cancer and the patient population most 'at risk' is known to rarely attend for oral examination or regular dental care (Scott et al 2009).

General population screening programmes for oral cancer have been recognized to be fundamentally flawed as health care interventions for similar reasons. However, a more pragmatic approach may be to specifically identify and then target individual patient groups deemed to be at 'high risk' of developing cancer. Thus, focused oral cancer screening, specific health care information and treatment interventions should all target the 'at risk' populations (Williams & Bethea 2011); this is an important practical application of the treatment intervention discussed later in this thesis.

The ultimate and fundamental clinical management goal must, of course, be the prevention of cancer and all 3 classic tiers of preventive medicine are intrinsically linked throughout the process of diagnosis and management. Primary prevention, to entirely avoid disease development, concentrates on eliminating the principal risks factors of disease and promoting protective behaviour within a community or population; this clearly includes eliminating the use of tobacco products, avoiding excessive alcohol consumption and

improving diet and nutrition. Secondary prevention, to detect premalignant or early malignant disease at a stage when intervention leads to either cure or significantly reduced morbidity and mortality, requires an effective interventional management strategy. Tertiary preventive strategies attempt to reduce the risk of disease recurrence and minimize disease-related complications, and require appropriate clinical service provision for 'at risk' patients (Thomson 2012c).

An interesting but alternative viewpoint was proposed by Esserman et al (2013) who emphasized potential danger in over-diagnosis and over-treatment of 'indolent lesions of epithelial origin', defined as clinically recognizable lesions never likely to proceed to invasive or metastatic cancer. Whilst this may have validity in general screening programmes, for some breast or prostate intraepithelial neoplasms for example, the reality remains that oral squamous carcinoma is a particularly lethal and progressive disease and far too many patients present with advanced, locally invasive, and ultimately incurable metastasizing disease.

Previously available scientific literature has struggled to resolve the fundamental question whether early diagnosis and treatment of oral potentially malignant disorders will actually prevent the development of invasive cancer. It is not, however, an unreasonable hypothesis and as such has provided the direct stimulus and catalyst for the clinical research work presented in this MD thesis.

1.5 Current Problems in Diagnosis and Management

There are many problems in contemporary clinical practice associated with both diagnosis and interventional management for potentially malignant disease, and these are summarized in Table 1.3 (Thomson 2012c).

TABLE 1.3: PROBLEMS ASSOCIATED WITH DIAGNOSIS AND MANAGEMENT OF POTENTIALLY MALIGNANT DISORDERS

DIAGNOSTIC DILEMMAS	CLINICAL MANAGEMENT ISSUES
Confused terminology	Treatment aims are unclear
Non-specific diagnoses	No agreed treatment protocols
Lack of diagnostic consistency	No relevant randomised controlled trials
Clinical behaviour of lesions unpredictable	Clinical outcome data vary
Disease progression variable	Medical management is unsuccessful
Poorly defined clinical outcomes	
Unpredictable risk of malignancy	

The lack of relevant clinical trials in oral potentially malignant disorder management has posed a significant challenge in rationalizing contemporary clinical practice. High-quality randomised trials are, of course, important in ensuring effective comparison of treatment methods by limiting bias and confounding influences and remain fundamental to establishing meaningful systematic review evidence (Pandis 2013).

In clinical practice, the condition of 'potential malignancy' is a difficult concept to define so it is unsurprising that proposed treatment interventions appear non-specific with poorly-specified goals and no clear end-points; the few

clinical trials reported in the literature have concentrated on medical therapies and suffer from small patient numbers and short study durations which question the ultimate significance of their results (Lodi et al 2006, Lodi & Porter 2008). It is also unhelpful that none of the studies have ever demonstrated long-term lesion resolution, reduction in disease incidence or prevention of malignant transformation (Ribeiro et al 2010).

Despite the theoretical advantage of a chemopreventive strategy, no successful medical intervention has been established for potentially malignant disease management (Boyle 2001, Boyle 2004, Papadimitrakopoulou et al 2008, Ribeiro et al 2010, Mandal et al 2014, Dionne et al 2014). Mehanna et al (2009) and Dost et al (2014) have both concluded that effective treatment is likely to be based upon surgical excision of identifiable precursor lesions and thereby the eradication of visible manifestations of dysplastic mucosal fields. Balasundaram et al (2013) noted that, whilst there is little controversy in the literature regarding the need for intervention in severely dysplastic lesions (which probably possess the greatest risk of malignancy) opinion remains divided over the use of clinical observation versus treatment for lesions exhibiting mild to moderate dysplasia.

Brennan et al (2007) stated, somewhat unhelpfully perhaps, that due to a lack of randomized controlled trials, no evidence-based recommendations could be provided for either surgical or non-surgical treatment interventions for oral dysplastic lesions. In the absence of evidence-based treatment protocols or meaningful randomized controlled patient intervention trials, therefore, the longitudinal patient cohort study and clinical outcome data presented as an integral part of this MD thesis offer a unique opportunity to study a coordinated diagnostic and interventional management strategy for potentially malignant disorders.

1.6 Objectives of Potentially Malignant Disorder Treatment

Marley et al (1996, 1998) first highlighted the significant variation in management protocols for potentially malignant oral lesions that existed in the UK between different clinicians, and these observations have been confirmed by Kanatas et al (2011) and Kumar et al (2013) who note that there is still limited consensus on appropriate treatment. Arduino et al (2013) summarized the difficulties inherent in early diagnosis, detection and management of potentially malignant disorders, particularly emphasizing the lack of agreed pathological and diagnostic predictors and the need for long term patient studies to improve understanding of the natural history of these lesions.

Limited understanding of the progress of potentially malignant disease and a lack of meaningful, randomized controlled clinical trials thus pose significant challenges in rationalizing contemporary clinical practice resulting in a variety of proposed treatments essentially based upon clinicians' preferences and experience. In addition, the objectives of treatment intervention are poorly defined and rarely discussed in the literature, although most authors agree that prevention of malignancy is the main priority (Thomson 2012c).

It is, however, possible and highly pertinent to define a number of salient management goals in treating oral potentially malignant disease (Thomson 2012c, 2014); these are listed in Table 1.4 and discussed in the following sections.

TABLE 1.4: MANAGEMENT GOALS IN TREATING ORAL POTENTIALLY MALIGNANT DISORDERS
Accurate and definitive diagnosis Early recognition of malignancy Removal of dysplastic mucosa Prevention of recurrent or further dysplastic lesions Prevention of malignant transformation Minimal patient morbidity

1.6.1 Accurate and Definitive Diagnosis. Accurate diagnosis is fundamental, but incision biopsies are unlikely to be representative of the true nature of oral dysplastic lesions, particularly large and widespread disorders (Lumerman et al 1995, Cox et al 1999, Goodson et al 2011). Pentenero et al (2003) noted an 'under-diagnosis ratio' of 23.9% following incision biopsy of 46 potentially malignant lesions, whilst Holmstrup et al (2007) similarly commented that premalignant lesion biopsies were not always reliable, noting that 35 out of 101 excised premalignant lesions demonstrated more severe histopathological diagnoses compared with initial incision biopsy. Lee et al (2007) also observed 'under-diagnosis' in 29.5% of cases following comparison of incision biopsies with resection specimen analysis in 200 lesions. It is thus increasingly recognised that complete excision and histological examination of the entire clinical lesion is necessary to establish accurate dysplasia grading and definitive diagnosis (van der Waal 2009a, Thomson 2014).

In a series of Newcastle patient cohort studies, we have previously shown that excision biopsy following laser surgical treatment allowed more definitive histopathological diagnoses compared to initial incision biopsies which required 'up-grading' in 14 to 28% of cases due to increased dysplasia severity seen in excision specimens (Thomson & Wylie 2002, Hamadah &

Thomson 2009, Goodson & Thomson 2011). van der Waal (2009a) effectively summarized these data by stating that incision biopsy provides only a 'provisional' dysplasia diagnosis and that surgical excision of potentially malignant lesions in their entirety should be deemed mandatory for definitive diagnosis and grading. Balasundaram et al (2013) recently concurred that all potentially malignant disorders, regardless of clinical appearance or incision biopsy diagnosis, should be treated by whole lesion surgical removal.

1.6.2 Early Recognition of Malignancy. Formal surgical excision of potentially malignant lesions may facilitate early recognition of cancer. Einhorn & Wersall (1967) were among the first authors to highlight the importance that surgical removal of mucosal lesions might have in identifying early cancer undetected by incision biopsy, whilst Chiesa et al (1986) found unexpected malignancy in 6 out of 59 (10.2%) cases of excised potentially malignant lesions. Holmstrup et al (2007) noted that 7% of surgically excised premalignant lesions harboured a carcinoma, although there was a long time interval (mean 10.4 months) between initial incision biopsy and lesion removal in this retrospective study. Lee et al (2007) reported that 24 out of 200 patients (12%) who had undergone single-site biopsy demonstrated a malignancy upon whole precancer lesion excision, but that this fell to only a 2.4% unexpected carcinoma rate when multiple incision biopsies were taken from a lesion pre-operatively.

We found pre-existing 'unexpected' carcinomas in 15 out of a consecutive series of 169 potentially malignant disorder patients (9%), who were all treated for lesions diagnosed as exhibiting dysplasia only on incision biopsy. The true efficacy of interventional treatment was confirmed by the observations that all laser surgery excisions were carried out within 6 weeks of initial biopsy, the fact that none of the patients required additional post-laser treatment for their excised carcinomas and that all patients remained disease free at 36 months follow-up (Goodson & Thomson 2011).

Ho et al (2013) recently reported early detection of 23 squamous carcinomas by long-term monitoring of 91 oral epithelial dysplasia patients in a specialist clinic, although there was no standardized treatment intervention for this retrospective study and 19 cases were only diagnosed when biopsy was prompted by clinically apparent malignant change.

1.6.3 Removal of Dysplastic Mucosa. Oral potentially malignant disorders are, by definition, mucosal conditions and do not require the aggressive treatment necessary for removal or destruction of invasive cancer. It seems self-evident, therefore, to intervene early and remove dysplastic mucosa at a 'pre-invasive' stage. Surgical treatment has become increasingly recommended by a number of workers (van der Waal 2009, Mehanna et al 2009, Dost et al 2014), whilst others question whether surgical excision can reduce the risk of PMD recurrence or malignant transformation (Lodi & Porter 2008).

Surgical intervention for oral mucosal lesions may be carried out by conventional scalpel excision, cutting diathermy or photodynamic therapy but the efficacy of dysplastic tissue removal by CO_2 laser surgery has been confirmed in 2 patient cohort studies in which dysplasia-free or small residual foci of mild dysplasia only were seen in three quarters of treated cases (Hamadah & Thomson 2009, Diajil et al 2013). Whilst the precise techniques of laser excision will be described later in this thesis it is also noteworthy that, due to the standard practice of laser ablating oral cavity margins for 2 to 3mm beyond the excision margin during the final stage of treatment, no significant association has been seen between residual dysplasia in resection margins and clinical outcome (Thomson 2014).

Thermal cytological artefacts, including superficial vacuolation, detachment and shredding of keratin, basal cell degeneration and pseudodysplastic epithelial changes, have all been reported following CO_2 laser excision biopsies (Seoane et al 2010), but these do not appear to adversely affect histopathology assessment and reporting by experienced oral pathologists.

1.6.4 Prevention of Recurrent or Further Dysplastic Lesions. We have previously defined a range of specific clinical outcomes following potentially malignant disorder treatment including: clinical resolution (disease free status), persistent, recurrent or further PMD disease, malignant (same site) transformation and oral cancer development (at new sites); Thomson (2012d, 2014). Many authors now concur that consistency amongst defined diagnosis and treatment outcome categories is essential to inform future studies and ensure improved understanding of the natural history of oral potentially malignant disorders (Napier & Speight 2008, van der Waal 2009a).

Table 1.5 tabulates outcome data for 4 Newcastle cohort studies; whilst follow-up periods ranged from 4 to 10 years post-treatment, percentage outcomes for the categories remain remarkably similar between studies. Mean outcome data show that 68% of patients are disease free, 14% develop recurrent disease, 13% further disease, 2% undergo malignant transformation and 3% develop cancers at new oral sites.

It is difficult to find meaningful data with which to compare these studies as many of the papers in the literature are anecdotal, observational and retrospective in nature with no defined patient cohorts, heterogeneous lesions, and uncoordinated management and follow-up regimes. An important, consistent observation, however, is that the incidence of recurrent or further disease increases with the length of patient follow up, and that non-homogeneous leukoplakias, larger lesions, more severe dysplasias and floor of mouth and ventral tongue sites appear to be at greatest risk (Diajil et al 2013).

Smoking and alcohol remain persistent risk factors in patients following laser surgery and risk the development of further lesions. It is important to note, however, that we have also found high rates of further PMD disease in non-smokers and non-alcohol drinkers, which emphasizes the complexity of risk assessment and the probable importance of genetic predisposition and 'other' risk factors in precancer disease (Hamadah & Thomson 2009, Diajil et al 2013).

TABLE 1.5: CLINICAL OUTCOME DATA FOR INTERVENTIONAL LASER SURGERY (NEWCASTLE COHORT STUDIES)

	Thomson & Wylie (2002)	Stocker et al (2005)	Hamadah & Thomson (2009)	Diajil et al (2013)
Clinical Resolution (%)	76	67	64	62
Recurrent Disease (%)	6	15	18	18
Further Disease (%)	12	14	14	14
Malignant Transformation (%)	4	0	0	5
OSCC Development (%)	2	4	4	2
No. of Patients	57	199	78	100
Study Period (Years)	4	7	10	10

1.6.5 Prevention of Malignant Transformation. The risk of malignant transformation for oral potentially malignant disorders remains unpredictable and highly variable; Arduino et al (2013) reviewed 25 papers published between 1967 and 2011 and quoted an overall range for transformation of leukoplakia varying from 0.13 to 36.4%. van der Waal (2009) noted that, probably due to an inherently severe level of pre-existing dysplasia, the vast majority of erythroplakias will undergo malignant transformation although the paucity of documented case series precluded estimation of transformation rates. High rates of transformation, varying between 70 to 100%, have also been quoted for proliferative verrucous leukoplakias which, albeit controversially, are recognized as distinct, high risk multiple-site oral lesions (van der Waal & Reichart 2008).

It is a fundamental hypothesis of this thesis, and probably the most significant reason for actively treating potentially malignant disease, that surgical excision of dysplastic lesions should reduce the risk of malignant transformation. Lumerman et al (1995) observed a 6% rate of malignant transformation in patients who had lesions excised, compared with 15% in those who received no treatment. Schepman et al (1998), on the other hand, compared the incidence of oral carcinoma in both treated and untreated leukoplakia patients and observed little difference in malignant transformation risk.

Lodi & Porter (2008) have postulated that the natural history of potentially malignant lesions may be independent of treatment intervention, and that there may be a 'subgroup' of lesions inevitably destined for cancer development, irrespective of treatment intervention, although this does seem a rather negative perspective.

Whilst recognizing the inconsistent and unpredictable 'natural history' of potentially malignant disorders, Napier & Speight (2008) highlighted a particular increased risk of malignancy in older patients, females, non-smokers, dysplastic lesions arising on the tongue, floor of mouth and retromolar/soft palate complex, lesions of large size, those appearing non-homogeneous in nature and those of long duration. They concluded that accurately predicting which patients or lesions will develop carcinoma remains impossible in contemporary clinical practice.

Mehanna et al (2009) reviewed 14 un-related, non-randomized studies reporting on 992 potentially malignant disorder patients and quoted an overall malignant transformation rate of around 12%. Whilst mild to moderately dysplastic lesions showed a 10.3% transformation rate, this increased to 24.1% for severe dysplasia. Patients whose lesions were not excised exhibited a much higher transformation rate of 14.6% compared with only 5.4% for patients whose lesions were removed. Perhaps of most significance, however, was the 25% transformation rate observed in a UK specialist dysplasia clinic reported by Ho et al (2012), in which despite long

term patient follow up there appeared to be no coordinated treatment or interventional protocol in place.

Newcastle patient cohort studies of interventional laser surgery for dysplastic lesions have shown much lower malignant transformation rates, of between 2 to 5% depending on whether same site or new site cancer formation was examined, and certainly support the hypothesis that appropriate intervention reduces the risk of cancer development (Thomson & Wylie 2002, Hamadah & Thomson 2009, Diajil et al 2013). It is pertinent, in contrasting these low transformation rates with those in the literature, to emphasize that the Newcastle patients in these studies were treated for significant dysplastic disease, whereby 32 to 55% of lesions exhibited severe dysplasia or carcinoma-in-situ in initial incision biopsies (Thomson 2014).

Surgical excision of dysplastic lesions appears to decrease the risk of same site malignant transformation (Arnaoutakis et al 2013), but does not eliminate the risk of new site oral cancer development (Kumar et al 2013, Dost et al 2014). The clinical consequence is the realization that continued patient surveillance, regular clinic monitoring and risk factor profiling remain pertinent for all potentially malignant disorder cases following treatment (Thomson 2012d&e).

1.6.6 Minimal Patient Morbidity. For interventional treatment to become the management of choice for potentially malignant disorders, it is important that post-operative morbidity is low. Fortunately, significant complications following CO_2 laser treatment appear to be rare and, whilst some patients report post-operative pain, submandibular salivary gland swelling following floor of mouth procedures and lingual nerve dysaesthesia after tongue surgery, these are all usually transient and self-limiting and only rarely require additional treatment (Thomson & Wylie 2002, Goodson et al 2012). A small number of patients experience more severe or longer lasting complications but these are usually cases who have undergone more extensive surgery or who have continued to smoke heavily and consume alcohol after treatment (Goodson et al 2012).

In general, the use of CO_2 laser surgery is well tolerated and accepted by patients, aids haemostasis, promotes excellent healing and produces minimal scarring with little functional deficit or patient morbidity. A particular advantage is the ability to repeat excisions or ablations at the same site without compromising oral healing or function (Thomson 2012c).

Ho et al (2013) recently reinforced the value of intervention in potentially malignant disorders to facilitate detection of oral carcinomas at an early stage, thus enabling curative treatment with simple and minor surgical interventions. Increasingly, the use of trans-oral laser microsurgery is being applied more widely in head and neck surgery to reduce morbidity, whilst maintaining efficacy, of tumour resection procedures (Werner et al 2002, Thomson & Goodson 2015).

1.7 Interventional Laser Surgery

Interventional laser therapies have evolved following demonstrable failure of observational or medical therapies and the limitations of conventional surgery in treating oral cavity potentially malignant disease. Laser is an acronym for 'light amplification by stimulated emission of radiation' and the laser device emits a monochromatic, coherent wave of light energy delivered to target tissue via fibre-optic systems or a series of articulated arms and mirrors. A photo-thermal reaction occurs when laser light interacts with tissue; between 60 to 100^0C coagulation facilitates localised haemostasis or tissue necrosis, whilst at 100^0C and above vapourisation allows the surgeon to incise tissue, and to either resect or ablate lesions (Thomson 2012c).

The carbon dioxide (CO_2) surgical laser has been used extensively in the treatment of oral mucosal lesions. Sealed CO_2 gas is the active medium generating laser light in the mid-infrared range at 10,600nm; as this is near the spectroscopic absorption peak for water, all oral soft tissues successfully interact with the CO_2 laser beam (Jerjes et al 2012a & 2012b,Thomson 2012c).

Figure 1.4 summarizes the surgical excision of a buccally-sited potentially malignant mucosal lesion using the CO_2 laser; a hand-held delivery device, with a laser spot size of 1mm diameter, is used. A helium-neon aiming beam facilitates guidance to the target and an evacuation system removes smoke and debris from the surgical site.

Single pulse laser mode is used to outline resection margins, which are situated at least 5mm outside the apparent clinical margins of the target lesion. Although it is recognised that excision margin placement is based upon subjective judgement by the operating surgeon, we have not found adjunctive visual examination techniques to helpfully influence the intra-operative siting of resection margins or to significantly improve the achievement of disease-free resection margins (Thomson et al 2010, Goodson & Thomson 2014). Pulse marks are connected using the laser in a continuous mode, deepening the incision to approximately 5mm in the sub-mucosal plane; Figure 1.4B.

Depth of excision is influenced by anatomical site, less when involving thin floor of mouth tissue or resections overlying alveolar bone, and by the extent of known dysplasia; severe dysplastic lesions are resected at a deeper level due to the risk of foci of micro-invasive or early invasive squamous cell carcinoma co-existing. The whole specimen is then resected by undercutting at a constant depth, as illustrated in Figure 1.4C, which demonstrates the buccinator muscle lying immediately beneath the excision specimen.

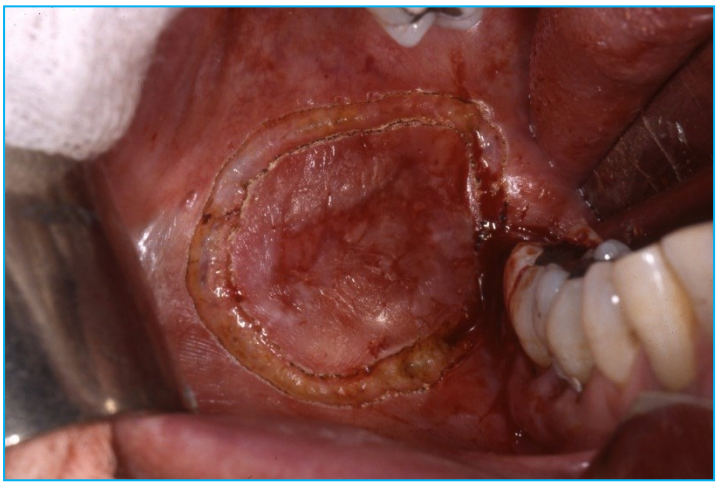
Following excision, the surgical bed and all peripheral margins are vapourised using a defocused laser beam to eliminate residual disease, facilitate haemostasis and to effectively extend the treatment field beyond the surgical excision zone; Figure 1.4D.

The excision specimen is sutured at one or two points to aid later tissue orientation, Figure 1.4E, and is then placed in formal saline solution prior to forwarding to the pathology laboratory for definitive histopathological analysis.

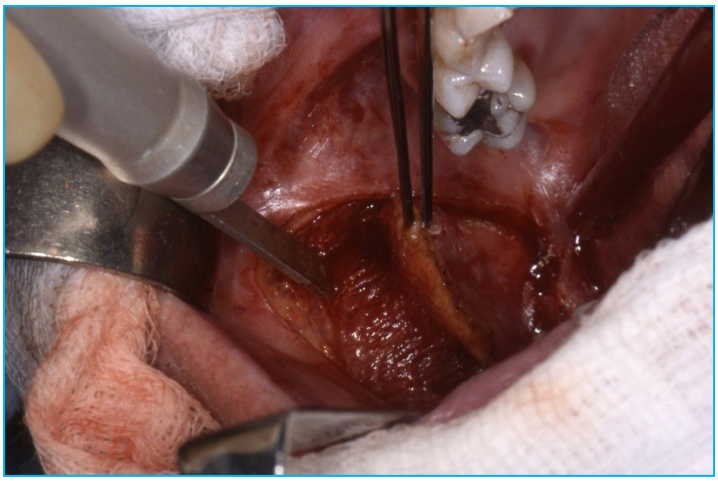
Figure 1.4: Interventional Laser Surgery Excision showing (A) erythroleukoplakic buccal mucosal lesion which demonstrated severe dysplasia on incision biopsy, (B) resection margins as marked out by CO_2 laser, (C) dysplastic mucosal lesion resected by laser at a constant sub-mucosal level, (D) appearance following post-excision laser vapourisation of lesion margins and base to eliminate residual mucosal disease and facilitate haemostasis, and (E) excision specimen prior to forwarding for histopathological assessment.

A

B

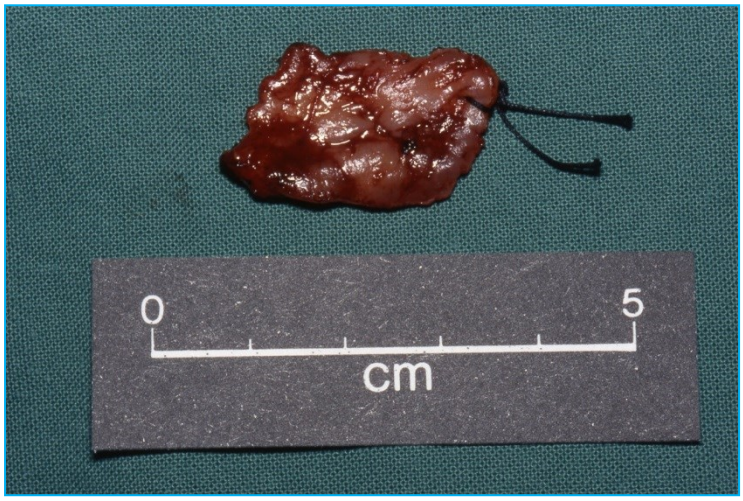


C



D

E



Clinically, there is little in the way of immediate post-operative pain, swelling or discomfort and patients are allowed to take clear fluids straight away, followed 2 hours later by a gradually increasing soft diet. Excised areas heal well by secondary intention, with a fibrinous cream coloured coagulum forming over the wound within the first few days followed by re-epithelialization from surrounding wound edges usually complete within 4 to 6 weeks; these features are illustrated in Figure 1.5 A and B. Due to the effects of laser vapourisation, a lack of mechanical trauma during surgery and the absence of wound suturing, scarring is usually minimal and excellent aesthetic and functional results ensue (Thomson 2012c); Figure 1.5 C.

Whilst excision techniques are preferred, there is a limited role for ablation therapy in which surface mucosa only is destroyed, to a varying depth selected by the surgeon and dependent upon the pathological lesion treated, using a defocused laser beam. Whilst ablation is not the treatment of choice, because tissue is not excised for histopathological examination and the most abnormal basal epithelium may be left in situ, such techniques do have a small role particularly in treating non-dysplastic or mildly dysplastic lesions on tightly bound down alveolar or gingival tissue where excision can result in slow or non-healing mucosa with painful areas of denuded and ultimately de-vitalised alveolar bone (Thomson 2012c). Figure 1.6 illustrates laser ablation destruction of a small patch of mildly dysplastic proliferative verrucous leukoplakia arising on the posterior maxillary gingiva.

Figure 1.5: Healing Following Interventional Laser Surgery Excision showing (A) immediate post-surgical appearance following excision of a dysplastic lateral tongue lesion and vapourisation of all surgical margins (see also Figure 4.1B), (B) 2 weeks post-laser with creamy fibrinous exudate and pink, healthy granulation tissue, and (C) healing at 2 months with minimal scarring, good appearance and excellent functional mobility.

A

B

C

Figure 1.6: Interventional Laser Surgery Ablation (Gingiva) showing (A) the pre- and (B) the post-ablation appearance of posterior maxillary gingiva, following superficial destruction of a patch of mildly dysplastic proliferative verrucous leukoplakia.

A

B

The technique of interventional CO_2 laser surgery as a treatment modality offers precise precancerous lesion excision, surgery administrable under general or local anaesthesia, full histopathological assessment of tissue specimens, minimal post-operative morbidity and, importantly, facilitates a coordinated and structured patient follow up and surveillance strategy to ensure early recognition of recurrent or further dysplastic disease or the development of cancer (Thomson & Wylie 2002, Goodson et al 2012, Thomson 2014).

There remains, however, a lack of evidence-based treatment protocols and meaningful randomized trials in potentially malignant disorder management. In a small, comparative cohort study we assessed the results of surgical intervention in 78 PMD patients deemed at 'high risk' of malignant transformation with observational management in 39 'low risk' cases and demonstrated that, whilst 64% of laser treated patients were disease free 3-years post-intervention, 77% of observed lesions persisted (Thomson et al 2009). Clearly limited in significance by its non-randomization, the study nonetheless supports the efficacy of laser as a treatment intervention.

Although a readily available, effective and low morbidity interventional treatment, specific evidence is lacking to support the role of CO_2 laser surgery role in reducing the risk of malignant transformation. Similarly, only limited data are available in the literature to determine overall length of individual patient follow up or the optimal time intervals between clinic appointments to monitor patients safely post-treatment. Many of these issues will be examined further in this MD thesis.

1.8 Oral Oncology in the North-East of England

The Department of Health in England emphasised the importance of early detection of malignant disease in their Cancer Reform Strategy (2007), and this seems especially pertinent for oral squamous cell carcinoma. The incidence of oral cancer has risen steadily in the UK, especially over the last decade, and a particularly strong association has been seen with social inequality and material deprivation (Greenwood et al 2003). In a similar study from India, low socioeconomic status was linked to increased tobacco usage, enhanced alcohol consumption, poor fruit and vegetable intake, and a resultant increased risk of potentially malignant oral disease (Hashibe et al 2003).

The general health of people living in Newcastle upon Tyne is worse than average for many of the parameters reported in England, with reduced life expectancy, high levels of adult smoking and smoking-related deaths, and significant rates of alcohol-related hospital admission being particularly pertinent to the themes explored in this thesis (Public Health England 2015).

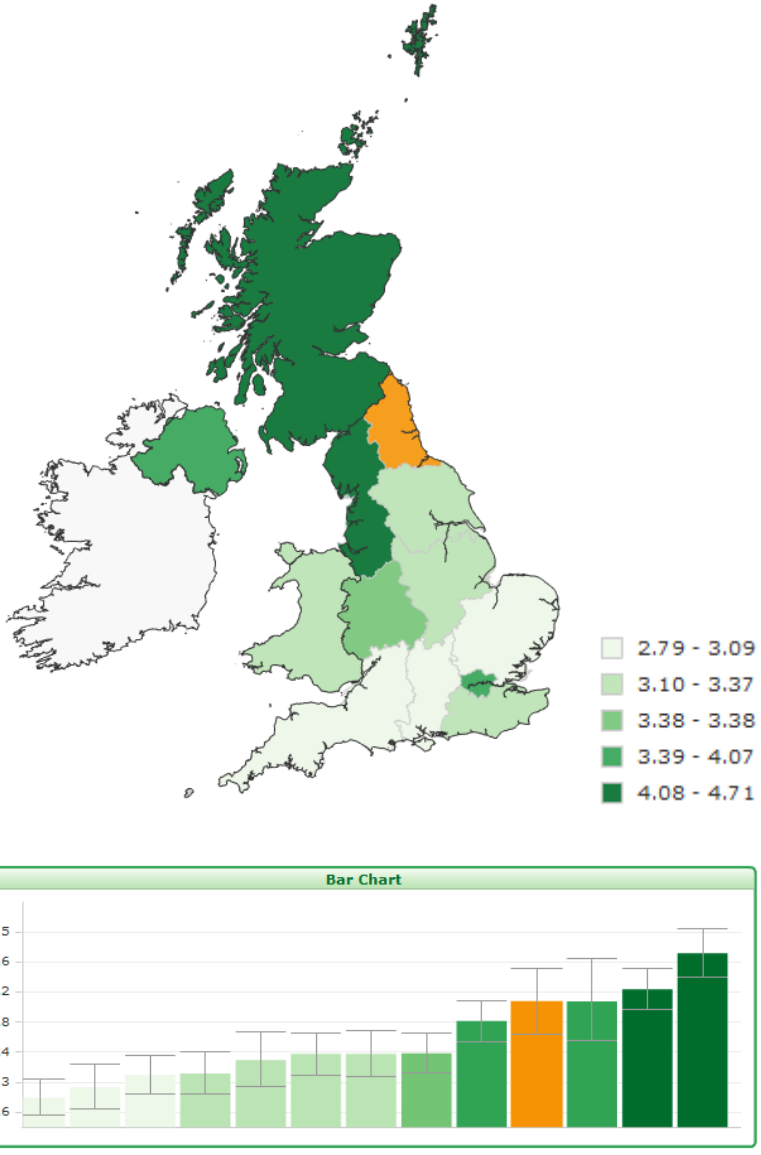
Unsurprisingly, a North-South divide in oral cancer incidence exists, especially for males, with the highest rates within England seen in the North. Figure 1.7 illustrates this with data from 2006-08 confirming a standardised rate for oral cavity cancer of 4.06 per 100,000 for North-East England, only exceeded by that within North-West England (4.23) and Scotland (4.71); National Cancer Intelligence Network (2014).

O' Hanlon et al (1997) previously reported an average annual number of new mouth cancer cases in North-East England of 47 males and 20 females, with 26 deaths in males and 11 in females each year; incidence and mortality were both confirmed to be greater in the North than in the rest of England and Wales.

With a regional North East population of approximately 2.6 million and a city population of around 280,000 (Office for National Statistics 2012), the hospitals comprising the Newcastle upon Tyne Hospitals NHS Foundation

Trust serve a large patient base distributed over a wide geographical area. Review of patient referral data for the Northern Head and Neck Cancer Unit at Freeman Hospital in Newcastle show that approximately 200 new head and neck malignancies are diagnosed each year, with around 45 oral cancers requiring treatment (McKie et al 2008). More recently, the Newcastle unit was characterised as undertaking a 'high' annual workload for major head and neck cancer surgery (Price et al 2014).

Figure 1.7: Oral Cancer Incidence in North-East England illustrating a standardised rate of 4.06 per 100,000 (orange labelling) for 2006-08; data and illustrations obtained from the National Cancer Intelligence Network website (2014).



It is interesting to note, however, that no data exist to document the incidence or prevalence of oral potentially malignant disorders in the North-East of England. Therefore, the best currently available information is based upon clinical records. The Newcastle potentially malignant disorder clinic was established in 1996 by this author, and is currently run on a weekly basis in the out-patient department of the Maxillofacial Unit at the Royal Victoria Infirmary. Approximately 1200 patient attendances occur annually comprising both new patient referrals of suspicious oral mucosal lesions, from both primary health care practitioners or from specialist colleagues in secondary care, and longer-term follow-up of previously diagnosed and treated cases (Thomson & Wylie 2002, Thomson 2012c). A specific objective of this thesis, therefore, will be to use anonymised clinic data to more fully characterise the presentation and management of oral potentially malignant disorder patients in North-East England.

1.9 Overall Aims and Hypotheses of the Thesis

The overall aim of the research work presented in this thesis is, in the absence of any formal, national oral potentially malignant disease statistics or a robust evidence-base, to profile patient demography and detail clinico-pathological data from patient cohorts presenting to a specialist, potentially malignant disorder service in a large university teaching hospital in Newcastle upon Tyne in North-East England, and to determine clinical outcomes for those patients treated primarily by interventional CO_2 laser surgery and to thereby attempt an assessment of the effectiveness of this treatment protocol and its influence on the progress of oral carcinogenesis.

A number of hypotheses will be tested:

1. Assessment of standard clinico-pathological features cannot predict disease progression or clinical outcome for oral potentially malignant disorders,

2. Incision biopsy techniques are insufficient for definitive histopathological diagnosis, which requires whole lesion excision for microscopic examination,

3. Interventional laser surgery is an effective tool for definitive diagnosis and effective treatment of potentially malignant lesions and,

4. Active intervention during the progress of ‘pre-malignancy’ halts the progress of oral carcinogenesis and reduces the risk of cancer development.

Chapter Two

PUBLICATIONS

Perspectives on Oral Potentially Malignant Disease

2.1. Introduction and Overview of Presented Publications

The diagnosis and management of oral potentially malignant disease involves a complex interaction between presenting patients and their information and management needs, clinicians' views on disease recognition and treatment, and histopathological assessment and diagnosis of mucosal biopsy specimens. Uncertainty regarding the concept of the 'potentially malignant state' remains a difficult and pernicious influence throughout this process. This chapter will explore all of these issues which, taken together, are a fundamental influence on clinical management strategies for patients with such disorders.

Three recent, pertinent publications and four relevant research papers dealing with contemporaneous aspects of each of these potentially malignant disorder management issues are presented in support of this MD thesis, and are now included in the chapter (where appropriate, in chronological order of publication) within each of the following 4 themes:

1. The Clinicians' Perspective (Publication 2.2)

2. The Patients' Perspective (Publications 2.3a, 2.3b and 2.3c)

3. The Pathology Perspective (Publication 2.4)

4. The Clinical Management Perspective (Publications 2.5a and 2.5b)

Each publication is preceded by a summary page detailing the background to the paper, the key message, overall paper significance and relevance to the thesis. The publications are followed by a discussion section.

2.2 The Clinicians' Perspective

Thomson PJ, McCaul JA, Ridout F, Hutchison IL. To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. *British Journal of Oral & Maxillofacial Surgery* 2015 53 : 1027-1031

Background: Current PMD management requires clinical recognition of suspicious mucosal lesions and incision biopsy to facilitate histopathological assessment of dysplasia, followed by excision of 'high risk' lesions and long-term patient surveillance to monitor for further disease. In the absence of treatment consensus, the aim of this study was to determine contemporaneous clinicians' views on available clinical management strategies.

Key Message: 251 UK clinicians participated in a web-link questionnaire demonstrating some agreement on how to manage individual PMD lesions and on treatment decisions for 3 different clinical scenarios. Whilst most favoured excision of severely dysplastic lesions and observation of mild dysplasia, clinicians' greatest equipoise in decision making was seen in patients with moderate dysplasia.

Paper Significance: This is a contemporaneous review of a substantive number of UK clinicians' views on diagnosis and management techniques for oral potentially malignant disease. In addition, this is the first paper to try to elicit clinician support and involvement in a proposed, prospective randomised clinical trial to investigate treatment efficacy.

Thesis Relevance: The approach to PMD clinical management presented and analysed later in this MD thesis evolved through a lack of universally agreed treatment protocols. Clinicians' views on PMD diagnosis and treatment, however, remain fundamental, not only to determine current practice in UK management strategies but also to ensure relevance, pragmatism and effective recruitment to support future clinical trial development.

2.3. The Patients' Perspective

2.3a Green RA, Exley C, Thomson PJ, Steele JG. Understanding patient views and experience of oral pre-cancer. *Journal of Dental Research* 2010 89B: 2571

https://iadr.confex.com/iadr/2010barce/webprogram/Paper132749.html

Background: Whilst many studies have examined quality of life issues related to oral cancer diagnosis and treatment, there is little in the literature regarding potentially malignant disease. Qualitative interviews were carried out with 16 North-East oral potentially malignant disorder patients to explore their views and treatment experiences.

Key Message: Patients varied significantly in their conception and misconception of their disease and its cause. The impact of the diagnosis on their lives and unmet information needs were consistent patient concerns. The individual clinician-patient relationship was deemed important, with patients particularly emphasizing the importance of 'expert' knowledge and consistency during their clinical management.

Paper Significance: This is an innovative study which has provided a unique insight into the potentially malignant disease treatment pathway from the patients' perspective. This research paper has been cited in the literature and continues to inform specialist practice.

Thesis Relevance: Challenges exist for clinicians throughout the process of diagnosis and management of oral potentially malignant disease, including the use of terminology, conveying information, recognising and then meeting patients' additional needs, encouraging behavioural change and rationalizing treatment decisions. These issues are pertinent when determining and reviewing clinical outcome data from patient cohort studies presented in this thesis.

2.3b Green RA, Thomson PJ, Exley C, Steele JG. Understanding the transition from primary to secondary care: experiences of patients with oral pre-cancer. *British Journal of Oral & Maxillofacial Surgery* 2011 49 Suppl. 1 : S60 doi:10.1016/j.bjoms.2011.03.105

Background: In a development of the study reported in paper 2.3a, data from 28 qualitative interviews with North-East England potentially malignant disorder patients were reviewed to characterise patients' experience of their individual progression through local healthcare systems, from initial primary care contact through to attendance at secondary care, specialist hospital services.

Key Message: Patients' accounts of their health care journey provided new and invaluable insights into the oral pre-cancer patient's journey. Timely referral to appropriate specialist care reduces patient uncertainty and helps allay feelings of 'powerlessness' during the health care journey.

Paper Significance: This is the first paper to directly elicit potentially malignant disorder patients' experiences of their management as they proceed from primary to secondary healthcare services.

Thesis Relevance: In developing a formal review of treatment intervention for oral potentially malignant disease, this paper offers an invaluable, additional perspective and detail regarding the patient's viewpoint of their clinical management pathway.

2.3c Green RA, Exley C, Steele JG, Thomson PJ. Patients understanding of the unknown: oral pre-cancer. *Journal of Dental Research* 2014 93B: 1515

https://iadr.confex.com/iadr/14iags/webprogram/Paper188348.html

Background: Following on from papers 2.3a and 2.3b, data from 28 qualitative interviews with North-East England oral potentially malignant disorder patients were analysed to specifically map individual patient health care journeys.

Key Message: Patients experienced significant uncertainty at a number of stages during their diagnosis, treatment and clinic follow-up. For many, such uncertainty was seen as a negative experience which impacted on both their working and social lives.

Paper Significance: This is the first paper to demonstrate the significance of uncertainty and its resultant impact upon patients' overall experiences of oral potentially malignant disease.

Thesis Relevance: From a patient perspective, the uncertainty inherent in a potentially malignant condition leads to a deleterious impact on many aspects of their lives. Opportunities exist throughout the patient journey at diagnosis, during interventional treatment and follow-up to ensure clarity and consistency in explanation and use of terminology. Recognising the significance of uncertainty in contemporary PMD management is important during review of study data presented in later chapters of this MD thesis.

2.4. The Pathology Perspective

Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ. Oral precursor lesions and malignant transformation – who, where, what and when? *British Journal of Oral & Maxillofacial Surgery* 2015 53 : 831-835

Background: Histopathological assessment and dysplasia grading of mucosal biopsies remains fundamental to assess malignant transformation risk in clinically recognisable oral potentially malignant lesions. The aim of this study was to evaluate the relevance of histopathological diagnoses of previously identified precursor lesions upon subsequent malignant transformation.

Key Message: By retrospectively reviewing 1,248 SCCs diagnosed in Oral & Maxillofacial Surgery Units in North-East England between 1996 and 2009, 58 previously biopsied same-site precursor lesions were identified. The single most common histopathological finding in 19 cases was lichenoid inflammation with no discernible dysplastic features.

Paper Significance: This study highlights limitations of incision biopsy diagnosis and dysplasia grading as predictive tools and supports the view that squamous carcinoma may arise in the absence of recognizable oral epithelial dysplasia. The paper also re-affirms the importance of clinical vigilance and active surveillance in the management of all clinically suspicious oral lesions irrespective of histological findings.

Thesis Relevance: Whilst the importance of effective communication between diagnostic pathologists and oral clinicians cannot be over-estimated in PMD management, dysplasia grading must be considered limited both as a diagnostic tool and as a predictor of clinical outcome. These particular issues will be explored further in the detailed patient cohort studies presented in this thesis.

2.5. The Clinical Management Perspective

2.5a Thomson PJ, Diajil AR, Goodson ML. Rationalizing risk assessment in oral potentially disorder management. *International Dental Journal* 2015 65 Suppl. 2 : 51

Background: This recently presented paper reports the results of a 300 publication literature review in an attempt to stratify known aetiological factors involved in oral carcinogenesis into 'high' and 'low' risk categories.

Key Message: Despite the absence of reliable predictive tools or biomarkers, integrating risk profiling to existing diagnostic and clinic protocols may prove a pragmatic tool to discriminate between 'high' and 'low' risk PMD patients.

Paper Significance: This is the first paper to delineate a 'high' risk PMD patient profile based upon the analysis of both lifestyle and medical and family histories.

Thesis Relevance: Whilst interventional surgical management appears a readily available, effective, low morbidity treatment, in the future we will need to definitively classify potentially malignant disorder patients into 'high' and 'low risk' categories and develop individually tailored treatment protocols. These issues will be further explored in this MD thesis.

2.5b Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6 : 186-191

Background: Recognising the significance of risk profiling outlined in paper 2.5a, this opinion paper expands upon the important concept of risk as it relates to initial diagnosis and subsequently throughout the overall management of oral potentially malignant disorders.

Key Message: An oral disease process characterised as 'potentially malignant', neither entirely benign nor frankly malignant, is a difficult concept for both clinicians and their affected patients.

Paper Significance: Whilst contemporary clinical practice struggles to predict individual PMD lesion behaviour, quantify risk for malignant transformation or objectively plan treatment intervention, recognising and addressing the uncertainty and unpredictability inherent in potentially malignant disease offers a strategy to objectify treatment protocols.

Thesis Relevance: It remains difficult in contemporary practice to quantify the risk of malignant transformation and predict clinical outcome. Further work in this thesis will examine treatment outcomes and cancer development in patient cohorts to try to improve understanding of the natural history of PMD disease and aid the development of objective and predictive diagnoses for future interventional management strategies.

2.6. Discussion

2.6.1. Introduction. The principal dilemma facing clinicians upon new patient presentation with an oral potentially malignant disorder (PMD) is to establish a definitive histopathological diagnosis and to confirm the optimal management strategy for that individual patient (Thomson 2014, Field et al 2015). As Field et al (2015) have pertinently observed, 'clinicians have a duty of care to patients to offer advice and management'. This is difficult, of course, when the evidence base for treatment guidelines is weak and knowledge limited by lack of relevant clinical trial data. Fundamentally, however, it remains important to attempt to identify individual patients and mucosal lesions at risk from the most progressive types of potentially malignant disease and, ultimately, those with the greatest likelihood of malignant transformation.

2.6.2. The Clinicians' Perspective. In Publication 2.2 we specifically sought contemporaneous views on individual clinico-pathological scenarios in order to ascertain clinicians' perspectives on management techniques for potentially malignant lesions. Questionnaire responses were received from 251 UK clinicians, making this one of the largest reported clinician surveys on PMD disease ever published.

Whilst most participating clinicians favoured excision of 'high-risk' severely dysplastic lesions and observation of 'low-risk' lesions, opinion was more divided for those disorders graded as moderately dysplastic, reflecting the prognostic uncertainty of 'mid-grade' dysplastic change. Although it is encouraging that a degree of consensus regarding management is apparent, the majority of responding clinicians were practising surgeons and therefore probably more likely to recommend intervention. The results also reflect an assumption, which may well be misplaced, that it is possible to reliably characterise some mucosal lesions as exhibiting 'low-risk' disease; this issue will be investigated further in this thesis.

Clinicians' views have been sought before, of course, initially in two papers by Marley et al (1996, 1998) who clearly highlighted a significant lack of agreement in PMD treatment decisions from 141 UK Oral and Maxillofacial Surgeons, whose management protocols included elimination of potential sources of mucosal trauma, prescription of anti-fungal agents, surgical excision, laser ablation and even radiotherapy treatment. Epstein et al (2007) similarly elicited a varying range of treatment responses including surgery, laser and cryotherapy, from 65 US Oral Medicine clinicians. More recently, Kanatas et al (2011) elicited the opinions of 199 UK surgeons regarding assessment, biopsy and follow-up of PMD lesions and found wide-ranging views and practice, with little in the way of consensus.

There are signs, however, that there may now be a move towards greater agreement supporting surgical intervention as the preferred treatment option for oral potentially malignant lesions, with increasing reports in the literature confirming efficacy of disease resolution and possible reduction in malignant transformation risk (Mehanna et al 2009, Thomson 2014). The evidence base supporting these concepts remains limited, however, and the important principles governing the interventional management of potentially malignant disease will be examined in detail later in this thesis.

2.6.3. The Patients' Perspective. The issues introduced in publications 2.3a, 2.3b and 2.3c, documenting patients' views and experience, are increasingly recognised as important, if not mandatory, issues in modern healthcare provision and research. It is interesting that, despite the inherent uncertainties that plague PMD diagnosis, treatment and follow-up, and particularly the lack of consensus-based clinical guidelines, patients clearly value and support 'expert' knowledge and opinion, especially when combined with a degree of consistency of approach to their individual management. These have always been core components of our Newcastle treatment philosophy and indeed are facilitated by the provision of dedicated and coordinated specialist services.

Green (2013) observed that patients' understanding of potentially malignant disease can be highly variable, however, and may be significantly influenced by the quality of communication with their clinicians and by the use of terminology. Whilst 'lay' terms are often favoured by clinicians in attempting to explain the concept and nature of pre-cancer disease, patients may well prefer and subsequently require more precise definitions and terminology in order to access supplemental information, especially via internet sources. It seems clear, therefore, that more attention is required to meet patients' information needs and to improve their overall understanding of potentially malignant disease. Green (2013) concluded that patients must be fully engaged in all aspects of their treatment decisions and necessary health-related behaviour changes for PMD management to become truly effective.

Ford & Farah (2013) recently emphasised the importance of exploring both the individual experience and the support needs of patients with oral potentially malignant disorders. van der Waal (2014) commented that clinicians may experience real difficulties in conveying PMD diagnoses and prognoses to patients, observing that whilst some patients will be able to balance uncertainties regarding treatment efficacy and morbidity, others will experience confusion and concern surrounding clinicians' inability to either predict or prevent malignant transformation. These latter observations, which have been experienced by the author in his own clinical practice and are explored in some detail in publication 2.5b, certainly support the research findings reported in publication 2.3c.

Assessment of patients' quality of life is also now regarded as an integral component of evaluating disease outcome, especially for chronic disease states and malignant conditions, including oral cancer (Tadakamadla et al 2015). In attempting a recent systematic literature review, however, Tadakamadla et al (2015) found a paucity of data regarding quality of life studies for patients with oral potentially malignant disease, despite the known significant effects such disorders inevitably have on oro-facial function, appearance and social interaction.

It is interesting in publication 2.3b that 'timely' referral from primary care to specialist services was found to be important to patients to help reduce anxiety and ensure appropriate patient engagement. We have previously examined the PMD management pathway for 100 Newcastle patients once entering specialist care and confirmed that efficient treatment times contribute to an overall successful management strategy (Diajil et al 2014). It remains difficult, however, to influence individual patients' initial presentation to primary care services or their subsequent referral times into specialist care. These issues will be explored in more detail later in the thesis.

The patient experiential studies reported in this thesis, particularly those highlighting patients' understanding of their disease, clearly demonstrate the numerous influences that may adversely affect patients during their PMD treatment journey and emphasise that these factors will require further study and greater attention in future clinical research work.

2.6.4. The Pathology Perspective. The role of the pathologist in PMD management has been described as firstly, to exclude benign disease processes and then secondly, to determine the presence and degree of epithelial dysplasia thus estimating the risk of cancer development (Speight & Torres-Rendon 2011). Publication 2.4 reports upon a retrospective histopathological study in which details of known oral mucosal precursor lesions, those that specifically preceded same-site invasive carcinoma development, were identified from laboratory databases and then characterised in detail. It is significant that in this study only 25 out of the 58 precursor lesions (43%) were actually shown to be dysplastic in nature, but of especial interest was the high number of non-dysplastic lichenoid lesions that progressed to carcinoma, the latter developing clinically into aggressive, advanced-stage malignancies.

The potential for malignant change to occur in oral lichenoid lesions has been recognised, but remained controversial, for many years. There is little doubt that red and white oral mucosal lesions, clinically resembling lichenoid disease, can exhibit dysplastic features on histopathological examination and

progress rapidly to invasive carcinoma (Lovas et al 1989, Thomson & Goodson 2012a), and indeed such a clinical presentation was illustrated in Figure 1.4A. It is also well recognised that both dysplasia and lichenoid inflammation can co-exist in oral lesions, and this certainly adds to the on-going uncertainty and debate surrounding the malignant potential of lichenoid lesions (van der Meij et al 2007, Patil et al 2014).

Regardless of clinical appearance, the histological finding of dysplasia within oral lichenoid disorders is probably the most salient diagnostic factor and such lesions should be regarded as 'high-risk' potentially malignant disease (Thomson & Goodson 2012a). It may well be that intense inflammatory cell infiltration of the immediate sub-epithelial tissue represents an enhanced immune response to antigenically disturbed dysplastic epithelium.

Notwithstanding the above, it is important to emphasise that despite consensus review and re-grading of biopsy specimens by experienced oral pathologists in Publication 2.4, 19 oral precursor lesions were confirmed to have exhibited hyperkeratosis and lichenoid inflammation only on histopathological diagnosis, with no evidence of pre-existing dysplasia.

In terms of its clinical relevance, therefore, Publication 2.4 clearly supports long term follow-up in specialist clinics for patients with clinically suspicious oral mucosal lesions, irrespective of histopathological diagnosis. This theme has been developed and reported on recently by a number of authors and will be discussed in more detail later in this thesis (Mehanna et al 2009, van der Waal 2014).

Of especial pertinence for the histopathological examination of PMD lesions, and thus an important feature of many of the subsequent studies to be discussed in this thesis, is the confirmation of substantial agreement between oral pathology specialists in Newcastle regarding biopsy diagnoses and grading of epithelial dysplasia. Substantive inter-observer agreement was seen (kappa = 0.642), as was agreement between original archival and study re-grading diagnoses (kappa = 0.825). Mullin et al (2015) recently reported upon the value of obtaining second opinions in pathology diagnosis,

especially specialist views, during the management of head and neck disease.

2.6.5. The Clinical Management Perspective. The concept of risk, as applied to the rational management of potentially malignant disease and discussed in Publications 2.5a and 2.5b, is both crucial in nature and fundamental to successful intervention and yet remains persistently obscure and highly variable in contemporary clinical practice. Risk stratification for malignant transformation relies on currently available clinical and histopathological assessments of suspicious oral mucosal lesions, but is frustratingly limited in practice by its highly subjective nature (Thomson 2014, Field et al 2015).

The dilemmas facing clinicians planning PMD treatment have already been discussed and summarized in Chapter 1. The inability to predict the individual behaviour of oral mucosal lesions and the difficulty in quantifying malignant transformation risk combine to render objective patient treatment planning extremely difficult. Whilst the clinical recognition of an oral mucosal abnormality may be relatively straightforward, the precise diagnosis ascribed to an individual PMD patient can be demanding, requiring detailed coordination of specific clinical and pathological data together with an attempt to distinguish ‘high risk’ from ‘low risk’ cases (Thomson 2012c).

Whilst many of these themes will be examined and discussed in more detail in the next chapters of this thesis, it is clear that the ability to integrate risk profiling into existing diagnostic, treatment and clinic surveillance protocols would provide an invaluable pragmatic tool to contemporary clinical management strategies.

2.6.6. Conclusions. Throughout the publications presented in this chapter is the central theme of a fundamental lack of understanding of the natural history of oral potentially malignant disease, which affects both clinicians and their patients; this was observed and emphasised by Napier & Speight (2008). In order to address the significant gaps in our knowledge, therefore,

the work presented in the next 3 chapters of this thesis will attempt, using observational and longitudinal cohort studies of PMD patient populations from North-East England, to delineate a better understanding of the clinical presentation, efficacy of interventional treatment and significance of long term follow-up of patients with oral potentially malignant disease.

Chapter Three

CLINICAL STUDY 1

Demography of Newcastle Potentially Malignant Disorder Patients

2015

3.1 Introduction

There are very few meaningful studies in the literature that address the specific epidemiology of oral potentially malignant disorders, so it remains difficult to report accurate incidence or prevalence data. Napier & Speight (2008) suggested a global prevalence rate of 1 to 5% for all potentially malignant disease, whilst Petti (2003) estimated a figure of between 1.5 and 2.6% for oral leukoplakia, the commonest potentially malignant lesion. Epidemiological studies such as these are often flawed, however, due to inconsistent diagnostic methodology, non-representative study populations and lack of confirmatory histopathological data (Thomson 2012a). This is compounded by the realization that no data exist at all to document either national or regional UK statistics.

The Newcastle Potentially Malignant Disorder (PMD) clinic was first established in 1996 by this author, initially in conjunction with the regional Oral and Maxillofacial Oncology service at Newcastle General Hospital and then from 2010 onwards as a specific, weekly clinic in the new out-patient Maxillofacial Unit at the Royal Victoria Infirmary (RVI). We have previously noted approximately 1200 patient attendances each year, which comprised new patient referrals of suspicious oral mucosal lesions, both from primary health care practitioners and specialist colleagues in secondary care, and longer-term follow-up of previously diagnosed and treated cases (Thomson & Wylie 2002, Thomson 2012c). Assuming a Newcastle upon Tyne population of around 280,000, an annual prevalence estimate of 0.43% may be made. This, however, is a rather crude calculation which does not discriminate between new patient presentations, review cases, or patient treatment episodes.

3.2 Aim of the Study

The aim of this simple, cross-sectional study, therefore, was to determine a more detailed demographic profile of a defined cohort of oral potentially malignant disorder patients attending for diagnosis and treatment at the specialist Newcastle upon Tyne Hospitals NHS Foundation Trust potentially malignant disorder clinical service during a 4 week period in 2015. In this manner, a comprehensive descriptive record of patient numbers, age, sex, oral lesions and interventional PMD management occurring in North-East England would be characterized.

3.3 Method

3.3.1. Caldicott Approval. Applying appropriate principles to creation of new, demographic and clinico-pathological oriented databases, formal Caldicott approval was obtained from the Joint Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust to collect anonymized data from medical records, operating logs and pathology reports from PMD patients treated by the author and attending specialist Oral and Maxillofacial services at the Royal Victoria Infirmary (Appendix I). Individual patient consent was not sought for data collection, because no patient identifiable material was used and no individual treatment, clinical intervention or clinical outcome was influenced by database construction and analysis.

3.3.2. Patient Demography. During 4 consecutive weeks in 2015, commencing Monday 12 January and finishing Friday 6 February, anonymized demographic and clinico-pathological details were recorded prospectively for consecutive patients attending clinics or undergoing surgery for oral potentially malignant disorders. Each patient was assigned a study number and the following data documented for each case: age, sex, smoking

and alcohol habits, reason for hospital attendance (new presentation, review patient or surgical treatment), clinical appearance (leukoplakia, erythroleukoplakia or erythroplakia) and anatomical site of oral mucosal lesions, whether single-site or multiple-lesion disease presentation, histopathology diagnoses, together with details of the treatment modality patients underwent (clinical observation, medical treatment or CO_2 laser surgery intervention).

3.3.3. Histopathology Diagnosis. All biopsy procedures on PMD patients were carried out, as deemed appropriate by well-defined existing management protocols (Thomson & Wylie 2002), in Oral and Maxillofacial Surgery clinics under the direction of the author and formalin-fixed tissue specimens subsequently assessed via standardized histopathology examination by experienced oral pathologists at the Royal Victoria Infirmary working to agreed diagnostic criteria (Sloan 2012). Using the World Health Organization (WHO) classification, specimens were graded into mild, moderate or severe dysplasia categories, carcinoma-in-situ (CiS) or squamous cell carcinoma (SCC); Gale et al (2005). In addition, the presence of hyperkeratosis, lichenoid inflammation (LI), or the diagnoses of proliferative verrucous leukoplakia (PVL) or chronic hyperplastic candidosis (CHC) were recorded.

3.4 Results

A total of 75 patients attended the Newcastle PMD service during the 4 week period. Detailed clinico-pathological data for this study group are listed in Appendix II. If patients presented with multiple lesions or had undergone more than 1 biopsy procedure, a single 'most significant' histopathological diagnosis was determined by the author from a review of the relevant clinical records for each case.

In terms of ethnicity, 74 patients (98%) were white European and 1 was Asian. The patient population included 46 males (with an age range of 41 to 83 years, and a mean of 60.9 years) and 29 females (age range from 29 to 85 years, with a mean of 58.1 years). The cohort varied between 13 to 26 patients per week and overall comprised 20 new referrals, 51 review patients and 4 surgical cases, as shown in Figure 3.1 and Table 3.1.

Figure 3.1: PMD Patient Attendances plotting the number of patients seen each week during the period 12 January to 6 February 2015 (w/c week commencing).

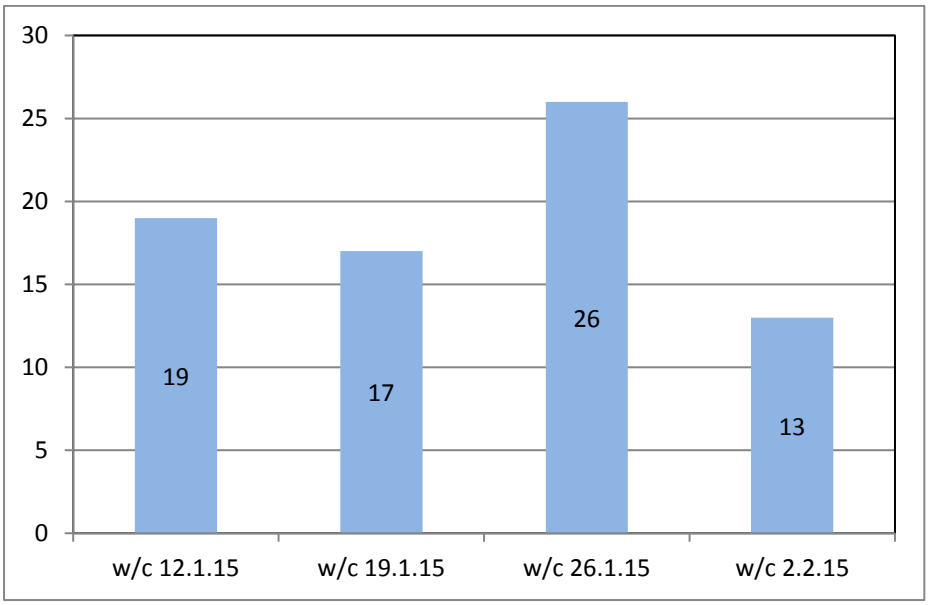


TABLE 3.1: REASON FOR PATIENT ATTENDANCE AT PMD SERVICE

Patient Activity	No. of Patients	%
New Patients	20	27
Review Patients	51	68
Patients Undergoing Surgery	4	5
Total	75	100

Although data relating to the numbers of cigarettes smoked per day or units of alcohol consumed per week were not fully completed for every patient in this study, the majority reported they currently smoked cigarettes or were recent ex-smokers (67%), as shown in Table 3.2, and all patients confirmed either regular or occasional alcohol consumption.

TABLE 3.2: SMOKING HABITS OF PMD PATIENTS

Current Tobacco Use	No. of Patients	%
Smoker	38	51
Ex-Smoker	12	16
Non-Smoker	25	33
Total	75	100

Table 3.3 shows that 84% of patients presented with oral leukoplakia, whilst erythroleukoplakia and erythroplakia were much less common; 11% and 5% respectively. Fifty patients (67%) presented with single-site disease and 25 (33%) exhibited multiple PMD lesions at distinct or bilateral anatomical sites; in 20 cases (27%) 2 sites were involved, whilst in a further 5 patients (7%) 3 sites were affected (full details are listed in Appendix II).

In total, 100 oral lesions were seen in the 75 patients and Table 3.4 lists the numbers at each anatomical site, together with the distribution of single and multiple lesion presentations. Overall, the floor of mouth and ventro-lateral tongue comprised the most commonly affected region (46%), with buccal mucosa next most common (14%). Multiple lesion disease appeared to present most frequently at gingiva/alveolus, buccal mucosa and floor of mouth sites.

TABLE 3.3: CLINICAL APPEARANCE OF PMD LESIONS

Clinical Appearance	No. of Patients	%
Leukoplakia	63	84
Erythroleukoplakia	8	11
Erythroplakia	4	5
Total	75	100

TABLE 3.4: ANATOMICAL SITE DISTRIBUTION OF PMD LESIONS

Anatomical Site	Total Lesions	Single Lesions	Multiple Lesions
Floor of Mouth	21	13	8
Ventral Tongue	11	9	2
Lateral Tongue	14	11	3
Tongue Dorsum	2	2	0
Buccal Mucosa	14	4	10
Labial Commissure	5	3	2
Labial Mucosa	2	1	1
Palate	9	7	2
Fauces	2	1	1
Retromolar Region	2	0	2
Gingiva	8	2	6
Alveolus	10	2	8
Totals	100	55	45

Following lesion biopsy, histopathological diagnoses were available for 74 patients (1 patient failed to return for biopsy investigation), and these are listed in Table 3.5. Although a total of 100 mucosal lesions were identified (Table 3.4), not all were biopsied and therefore a single, most significant, histopathology diagnosis was identified by the author and assigned to each patient. Whilst a wide range of diagnoses were recorded, the presence of epithelial dysplasia or carcinoma-in-situ was identified in the majority of cases (53 or 71%). In 17 cases a diagnosis of PVL, most commonly with the additional presence of dysplasia, was made.

TABLE 3.5: HISTOPATHOLOGY DIAGNOSES FOR PMD PATIENTS

Histopathology Diagnosis	No. of Patients	%
Unknown	1	1.3
Hyperkeratosis	4	5.3
Hyperkeratosis + Lichenoid Inflammation (LI)	8	10.7
Chronic Hyperplastic Candidosis	5	6.7
Proliferative Verrucous Leukoplakia (PVL)	2	2.7
Mild Dysplasia	20	26.7
Mild Dysplasia + LI	2	2.7
Mild Dysplasia + PVL	12	16.0
Moderate Dysplasia	10	13.3
Moderate Dysplasia + LI	3	4.0
Moderate Dysplasia + PVL	3	4.0
Severe Dysplasia	2	2.7
Carcinoma-in-Situ	1	1.3
Squamous Cell Carcinoma (SCC)	2	2.7
Total	75	100.0

Review of clinical management showed that the majority of patients, 52 (69%), had been treated by interventional laser surgery, 20 were managed by clinical observation alone and 2 were treated medically (systemic anti-fungal treatment for chronic hyperplastic candidosis); 1 patient failed to return following initial consultation (Table 3.6). During the 4-week study period, 4 patients attended theatre for laser treatment, primarily to excise dysplastic leukoplakia arising on the tongue (the latter data are summarized by study numbers 59 to 62 in Appendix II).

TABLE 3.6: PMD PATIENT MANAGEMENT

Management	No. of Patients	%
Interventional Laser Surgery	52	69
Clinical Observation	20	27
Medical Treatment	2	2.7
Did Not Re-Attend	1	1.3
Total	75	100

3.5 Discussion

3.5.1. Patient Numbers and Demographics. Seventy-five Newcastle PMD patients (55 review or treatment cases, and 20 new referrals) were identified during the 4-week study period; extrapolated over 12 months, this amounts to around 900 clinical cases, and is similar to un-published audit data obtained for the Maxillofacial Oncology / Dysplasia service during 4 weeks in January 2008 in which 97 cases, 17 new and 80 follow-up patients were identified (Ball 2008; Appendix III). These patient figures appear reasonably large in number when compared with Marley et al (1996) who reported that

the majority of UK Oral and Maxillofacial Surgeons saw less than 50 PMD patients per year and also more recently Kanatas et al (2011), in a questionnaire-based study of 199 UK surgeons, who reported even lower patient figures: only 38% of responding clinicians saw more than 30 new PMD patients per year, whilst a further 38% estimated they reviewed less than 30 in their clinics. In addition, the majority of clinicians (59%) did not provide designated, specialist clinics so the potential to concentrate expertise in diagnosis and management of their PMD patient cohorts must inevitably be reduced.

Overall, the patient group in this study appeared fairly representative of the Newcastle upon Tyne population, which has a self-reported ethnicity of 95% white British/Other and a median age of 41 years (Office for National Statistics 2012). Male patients, with a mean age of 60.9 years, accounted for 61% of the study group. Unfortunately, there are very few comparable data sets in the literature to compare these results, although Napier and Speight (2008) previously observed oral leukoplakia to be most common in males between the fourth and seventh decades of life. In an earlier UK study, Jaber et al (2003) reviewed 630 patients with dysplastic PMD lesions attending specialist Oral Medicine clinics in Southern England (Bristol and London) between 1972 and 1996 and found that 56% were male, with a mean age of 55 years. Warnakulasuriya et al (2011) reported on 1,357 PMD patients seen in Oral Medicine clinics at Guy's Hospital in London over a 10-year period in the 1990's, noting that the majority (61%) were female and that 70% were over 47-years of age; this cohort, however, comprised primarily patients with oral lichen planus and, as only 15% of oral lesions exhibited epithelial dysplasia, these data may not be wholly relevant or indeed comparable to the MD study group.

Worldwide, data is more difficult to interpret owing to significant variation in risk factor behaviour and disease presentation. In Brazil, Pulino et al (2011) analyzed biopsy results from 252 patients with suspicious oral lesions attending specialist clinics at the University of Sao Paulo over a 7-year period, but confirmed only 29 intra-oral PMD lesions (11.5%); mean age was

57.8 years, again with male predominance. Villa & Gohel (2014) identified only 27 PMD patients out of a total of 3,142 (0.9%) attending specialist diagnostic clinics at Boston University's School of Dental Medicine during an 8-month review, but similarly noted that males and current smokers were most likely to exhibit potentially malignant disease.

3.5.2. Clinico-Pathological Features. 63 patients in this study (84%) presented with oral leukoplakia, with floor of mouth and ventro-lateral tongue sites most commonly affected (46%); Jaber et al (2003) reported similar findings with around 42% of lesions arising on ventro-lateral tongue and floor of mouth sites, although only 50% presented as leukoplakia. In this study, both the labial commissure/buccal mucosal region and the palate/fauces/retromolar complex accounted for 19% of PMD cases, with gingiva and alveolar mucosa providing a further 18%; these sites accounted for 22%, 12% and 10%, respectively, of oral lesions reported by Jaber et al (2003). Napier & Speight (2008) usefully observed that PMD site is highly dependent upon both ethnicity and tobacco habit, with labial commissure/buccal mucosa particularly affected in South-East Asian patients using oral tobacco products and floor of mouth/ventral tongue sites more common in European populations smoking cigarettes.

Twenty-five patients (33%) presented with multiple-lesion disease, with the buccal mucosa, floor of mouth, and gingiva/alveolar mucosa most frequently involved (32 out of 45 lesions, or 71%); Appendix II and Table 3.4. We have previously shown multiple lesion disease to particularly affect buccal mucosa and floor of mouth sites (27 out of 54 lesions, or 50%) in a North-East population of 96 PMD patients (Hamadah et al 2010). There were no specific age, sex or tobacco use influences on disease presentation in either this or our earlier study (Hamadah et al 2010) but, as previously noted, comprehensive details relating to the amount of tobacco consumed were not available for all patients in this study.

A wide range of histopathological diagnoses were recorded for the 75 study patients and these have been summarized in Table 3.5. Overall, 53 patients

exhibited some degree of dysplasia on biopsy: 34 mild (64%), 16 moderate (30%) and 3 severe dysplasia or carcinoma-in-situ (6%); Jaber et al (2003) noted 47%, 29% and 24%, respectively, for these categories. Many of the lesions in this study exhibited, sometimes in combination with dysplasia, the varying presence of lichenoid inflammation (5) or proliferative verrucous leukoplakia (15). These later histological categories have, of course, become more pertinent in histopathology diagnoses in recent years, as previously discussed. In 2 cases (2.7%), squamous cell carcinoma was identified unexpectedly following laser excision of dysplastic lesions. We have previously reported a 9% incidence of unexpected carcinoma in laser excision specimens (Goodson & Thomson 2011) and such early diagnosis and treatment of invasive cancer provides strong evidence to support interventional treatment protocols (Dost et al 2014).

3.5.3. Patient Management. Having previously documented the interventional laser surgery protocol practiced in Newcastle (Thomson & Wylie 2002, Thomson 2012c), it is unsurprising that 52 study patients (69%) were treated by CO_2 laser: 48 attended for post-operative follow-up during the study period, with 4 actively undergoing surgery; Appendix II. Whilst no universal consensus on treatment exists, complete excision of 'high risk' lesions is recommended and most authorities now advise that surgical excision or ablation of identifiable lesions is likely to be more effective than observation, both for treating PMD disease and preventing progression to malignancy (Arnaoutakis et al 2013, Kumar et al 2013). The difficulty remains in defining precisely which oral mucosal lesions are 'high risk', and this is an important issue which will be further addressed in this thesis.

3.5.4. Limitations of the Study. Cross-sectional studies are, of course, disadvantaged by their 'snap-shot' nature and the potential for prevalence-incidence bias, although there does appear reasonable consistency through recent years when the data are compared with that from our 2008 study (Appendix III). A further limitation of this particular data set is the recognition that 'other' Newcastle PMD patients may have presented to alternate clinical services during the study period, including 'general' Oral and Maxillofacial

Surgery and other Dental or Oral Medicine clinics. It remains our experience, however, that over time the majority of Newcastle patients diagnosed with a potentially malignant disorder are referred during their 'treatment journey' to the specialist PMD service for advice and treatment (Green 2013).

3.6 Conclusions

The data collected in this study helps gain insight into the contemporaneous presentation and treatment of PMD disease in Newcastle upon Tyne, yet it remains a small 'snap-shot' of that activity. It is also disappointing for a specialist clinic service that comprehensive details of the amounts of tobacco and alcohol consumed were not recorded for every PMD patient at each clinic or treatment visit. Nonetheless, this study adds detailed information to our current knowledge base and may well help in the planning of future clinical service provision. It seems clear, however, that analyses of patient presentation, diagnosis and treatment over a longer time period is necessary to provide further and more detailed data regarding PMD disease in North-East England. Clinical Studies 2 and 4 reported later in this thesis will therefore utilize a retrospective cohort approach to delineate disease activity and clinical management strategies over a 19-year period.

Chapter Four

CLINICAL STUDIES 2 & 3

Use of Interventional CO_2 Laser Surgery in Newcastle

1996-2015

4.1 Introduction

Whilst there are no evidence-based guidelines or agreed treatment protocols for the management of oral potentially malignant disease, most authorities now agree that initial incision biopsy to identify dysplasia should be followed by whole lesion excision for definitive histopathological diagnosis and optimal treatment intervention (van der Waal 2009a, Dost et al 2014). Whilst a variety of surgical procedures have been proposed over the years, including scalpel excision, electro-surgery, cryotherapy, and photodynamic therapy, use of the CO_2 laser has become increasingly recommended due to the numerous reported side-effects and limitations of the other, afore-mentioned techniques (Ishii et al 2003, Mogedas-Vegara et al 2015).

The use of laser surgery as a treatment intervention for mucosal disease and the removal of oral soft tissue lesions has thus become an increasingly advocated procedure in the literature since first introduced into clinical practice in the 1970's (Tuffin & Carruth 1980, Frame 1984 & 1985, Frame et al 1984, Roodenburg et al 1991).

We have previously published a detailed management protocol for laser excision of oral dysplastic lesions, and also introduced and reviewed the indications and practical applications of this technique in Sections 1.6 and 1.7 of this thesis (Thomson & Wylie 2002, Thomson 2012c, Thomson 2014). Importantly, following a provisional diagnostic process and patient education regarding elimination of risk factor behaviours, interventional laser surgery facilitates precise precancerous lesion excision, minimally invasive surgery under general or local anaesthesia, full histopathological assessment of tissue specimens, reduced post-operative morbidity and coordinates patient follow up and surveillance strategies (Thomson 2014). Figure 4.1 illustrates the intra-operative use of the CO_2 laser by the author in the operating theatre.

Figure 4.1: Interventional Laser Surgery showing (A) CO_2 laser in use in the operating theatre for oral potentially malignant lesion treatment under general anaesthesia, and (B) intra-operative view during excision of dysplastic lateral tongue mucosa.

A

B

Ishii et al (2003) listed the significant, pragmatic advantages of laser surgery as a PMD treatment modality emphasising: improved haemorrhage control and excellent visibility intra-operatively, accurate excision due to reduced wound contractility during surgery, analgesia consequent upon sealing of local nerve endings, minimal damage to adjacent tissue thus reducing the post-surgical acute inflammatory response, reduction in scarring and contraction leading to excellent soft tissue mobility, minimal oral dysfunction and the ability to carry out repeated procedures. In contrast, quoted disadvantages of laser including slower re-epithelialization of oral wounds, occasional surface granuloma formation during healing (as demonstrated in Figure 4.2), and the technical intra-operative and associated laser safety requirements appear quite minimal in nature.

Figure 4.2: Post-Laser Surgery Appearance illustrating granulation tissue arising on the lateral surface of the tongue, often caused by irritation from the adjacent dentition during re-epithelialization. Whilst this resolves spontaneously over time, rapid subsequent healing is facilitated by a minor secondary procedure to excise the exuberant tissue.

Although Figure 4.1 illustrates the use of CO_2 laser surgery under general anaesthesia (GA), it is also practical to provide laser treatment under local anaesthesia (LA), especially for ablation procedures or the excision of smaller or more anteriorly-sited mucosal lesions, although in practice patients primarily undergo excision surgery to treat potentially malignant lesions and all are treated in the theatre environment to ensure optimal operating conditions and appropriate laser safety precautions (Thomson & Wylie 2002, Stocker et al 2005, Hamadah & Thomson 2009, Thomson 2012c).

This chapter will report on the results of 2 complementary clinical studies carried out to characterise the use of interventional CO_2 laser surgery to treat oral potentially malignant disorders in Newcastle upon Tyne between 1996 and 2015.

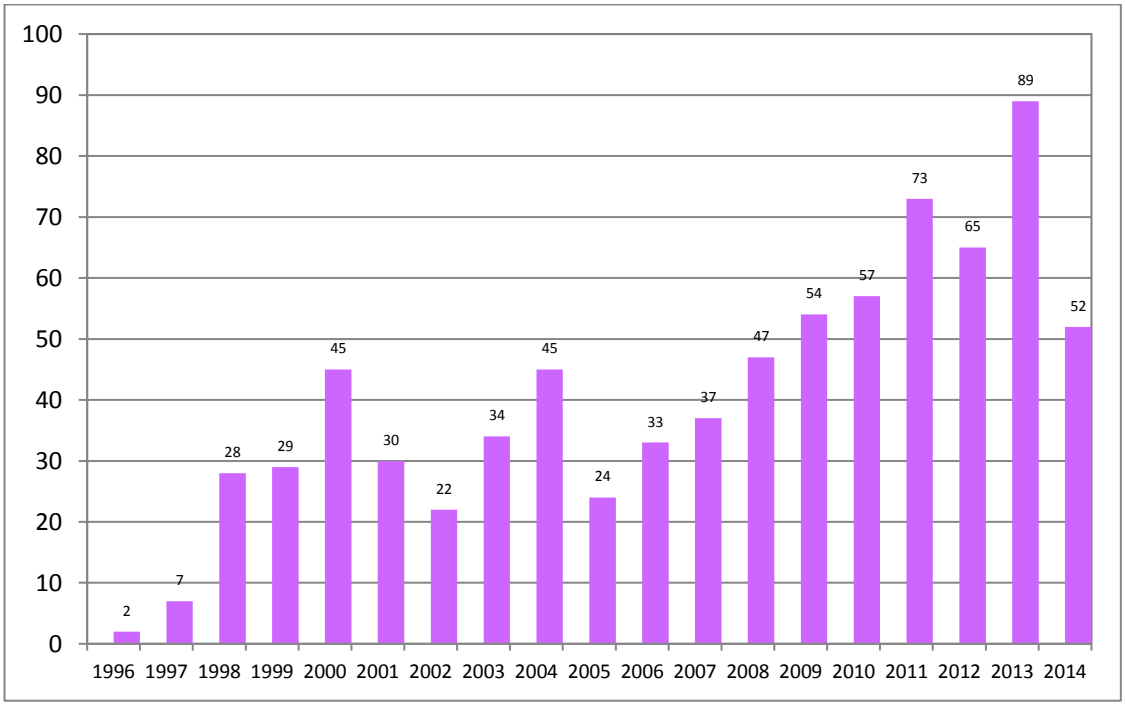
4.2 Clinical Study 2 – A Retrospective Review of Interventional CO_2 Laser Surgery in Newcastle 1996 – 2014

4.2.1. Aims. The specific aim of this retrospective study was to review the use of interventional laser surgery in the management of oral potentially malignant disorder patients by one surgeon using a standardised treatment protocol, as originally described by Thomson & Wylie (2002), over a 19-year period.

4.2.2. Method. A retrospective audit of Newcastle Oral and Maxillofacial theatre operating lists was undertaken to determine anonymized treatment details for patients attending for laser treatment of PMD disease between August 1996, when the author commenced clinical practice in Newcastle, and December 2014 (inclusive). All lesions underwent incision biopsy assessment prior to laser intervention, and both laser excisions and ablations were carried out, as deemed appropriate, by the same operator (PJT) working to standardised protocols with consistent diagnostic and treatment decisions (Thomson & Wylie 2002). It was not the intention of this study to document the demographics of treated patients, nor to record the clinico-pathological diagnoses for individual oral mucosal lesions or long-term clinical outcome and follow-up data which will all be detailed and analysed in depth in the clinical study reported in Chapter 5 of this thesis.

4.2.3. Results. In total, 773 CO_2 laser operations were carried out on 590 patients during the 19-year period, with a clear trend for increasing numbers of treatments to be performed through the years, as illustrated in Figure 4.3.

Figure 4.3: Number of Interventional Laser Surgery Operations carried out between 1996 and 2014, demonstrating a trend for increasing numbers of treatments to be performed during the study period.



Whilst the majority of patients, 513 (87%) required only 1 laser surgery intervention, 77 (13%) required multiple treatments most frequently 2 or 3 sequential procedures over time; these latter data are listed in Table 4.1 and graphically represented in Figure 4.4.

Laser excision (removing the entire visible mucosal lesion) was the preferred technique in 650 cases (84%), but as can be seen from Figure 4.5 a trend for increasing numbers of ablation procedures (superficial lesion destruction) was evident as the years progressed, with 123 (16%) ablations carried out in total. Figure 4.6 also reveals a similar trend for increasing use of LA for laser surgery, although most operations were still performed under GA (608 cases or 79%); only 2 cases were operated under local anaesthesia and intravenous sedation techniques.

TABLE 4.1: NUMBER OF LASER PROCEDURES PER STUDY YEAR

	No. Of Laser Procedures					
Year of Presentation	**1**	**2**	**3**	**4**	**5**	**>5**
1996	0	0	1	0	0	1
1997	5	1	1	0	0	0
1998	13	2	1	0	0	0
1999	22	2	1	0	0	0
2000	35	1	0	1	1	1
2001	21	1	2	0	0	0
2002	12	3	0	1	0	0
2003	24	2	2	1	0	0
2004	30	1	1	0	0	0
2005	13	0	0	0	0	0
2006	17	3	0	0	0	0
2007	22	2	2	0	0	0
2008	31	5	1	0	1	0
2009	35	2	2	1	0	0
2010	36	5	1	0	0	0
2011	50	8	4	0	0	0
2012	50	2	1	0	0	0
2013	64	8	0	0	0	0
2014	33	1	0	0	0	0
Totals	513	49	20	4	2	2

Figure 4.4: Numbers of Patients Undergoing More Than 1 Laser Surgery Operation. Whilst the number of procedures ranged from 2 to >5 (colour legend), most patients (69/77) required only 2 or 3 procedures; years 1996 to 2014 correspond with initial presentation date.

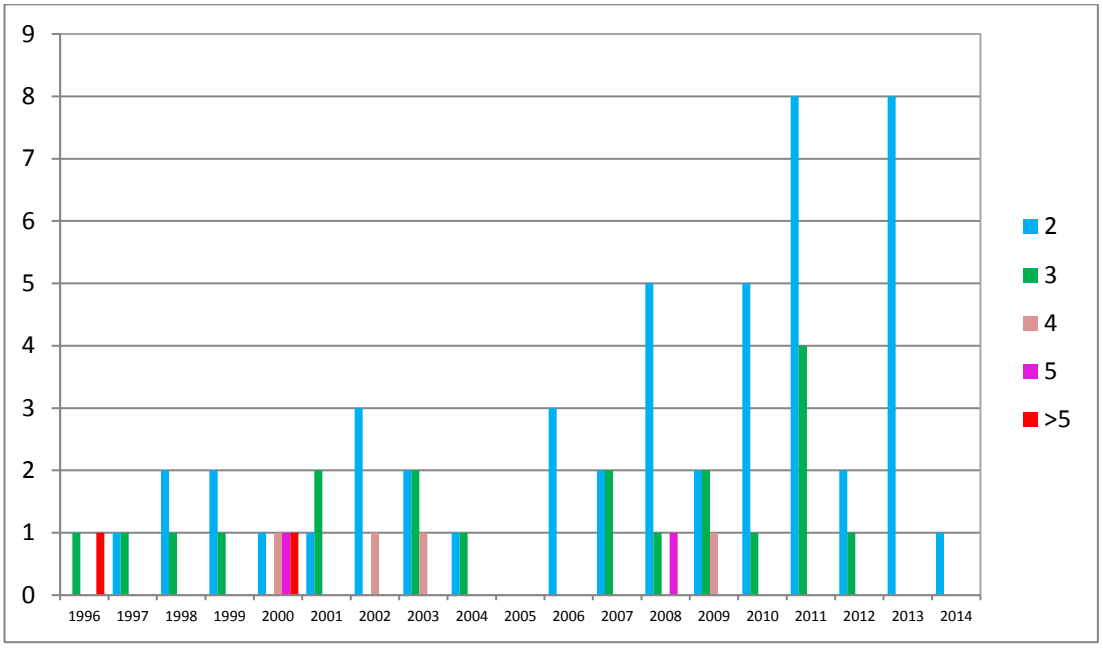


Figure 4.5: Number of CO_2 Laser Excision and Ablation Procedures carried out each year between 1996 and 2014 (total number of procedures = 773).

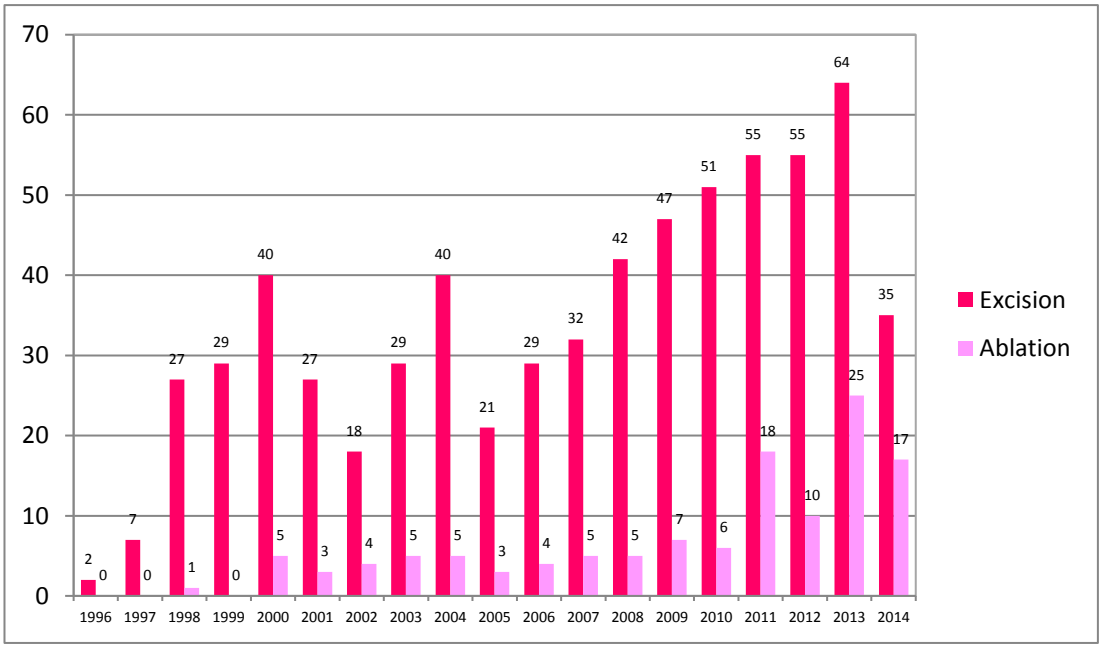
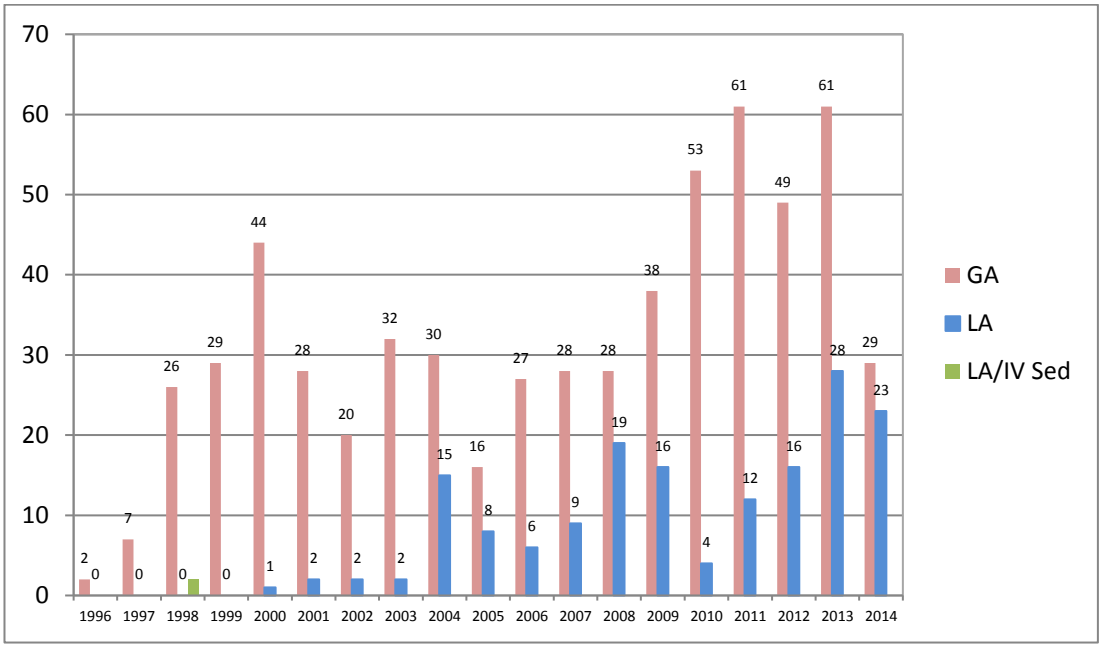


Figure 4.6: Type of Anaesthesia Used for CO_2 Laser Surgery each year between 1996 and 2014 (total number of procedures = 773); GA General Anaesthesia, LA Local Anaesthesia, LA/IV Sed Local Anaesthesia supplemented by intra-venous sedation.



4.2.4. Discussion.

(a) Interventional Laser Surgery. This study provides one of the largest interventional laser surgery data sets presented in the current literature; Jerjes et al (2012a), for example in one of the very few similar CO_2 laser studies in the contemporary literature, reported on only 123 laser procedures carried out on 77 patients during a 6-year study period at the Head and Neck Unit at University College Hospital in London.

It is clear from reviewing Figure 4.2 that the use of CO_2 laser surgery increased during the study period, peaking at 89 operative interventions in 2013. This undoubtedly reflects a steady increase in patient throughput through the Newcastle PMD service and probably an increasing trend to offer intervention to patients, although it remains unclear whether this reflects any rise in PMD disease incidence in the North-East over this time period.

The majority of patients (513) required only 1 laser treatment, although 77 underwent multiple treatments, ranging from 2 to more than 5, although most

commonly only 2 or 3 were required (in 69 patients); Table 4.1. In their study, Jerjes et al (2012a) observed that 62 out of 77 treated PMD patients required only one round of laser treatment, whilst a further 15 cases required up to 5 episodes of laser treatment during follow-up. Whilst the details of individual patient histories were not examined in this section of the MD study, the most common reasons for repeat laser treatment were recurrence of oral lesions (same site) or appearance of further lesions (new site) over time. We have previously summarized clinical outcome for cohorts of laser-treated Newcastle patients, demonstrating recurrent PMD disease in 6 to 18% of cases and further disease in 12 to 14%, as listed in Table 1.5.

Whilst a variety of lasers have been used to treat oral mucosal lesions, including higher potency and deeper penetrating neodymium:yttrium-aluminium garnet (Nd:YAG) and potassium-titanyl-phosphate (KTP) lasers, the CO_2 laser has become the preferred modality, primarily due to its ease of intra-operative use and its efficacy of oral soft tissue interaction (Thomson 2012c, Jerjes et al 2012b, Kumar et al 2013, Matsumoto et al 2015, Mogedas-Vegara et al 2015). Lim et al (2010) reported reduction in rates of oral leukoplakia recurrence when KTP was used instead of CO_2, but this was a small, retrospective ablative surgery study and did not examine the efficacy of laser excision.

We have previously reported upon common complications following intra-oral laser surgery in 82 treated PMD patients, including pain, bleeding, submandibular salivary gland swelling following floor of mouth interventions, and lingual nerve dysaethesia as a consequence of lateral tongue surgery, but most of these proved minor and transitory in nature resolving within the first few post-operative months (Goodson et al 2012).

Laser surgery is probably, therefore, the preferred treatment intervention for PMD because of its reliability and reproducibility, its ability to create relatively bloodless surgical fields, improved intra-operative accuracy and visualisation, reduced post-operative pain, limited scarring and reduction in damage to adjacent tissues, together with very low long-term complication rates (Lim et al 2010, Goodson et al 2012, Mogedas-Vegara 2015).

(b) Laser Excision versus Ablation. The fundamental distinction between laser excision and ablation techniques is the advantage of excision biopsy to facilitate histopathological analysis of mucosal lesions in their entirety, thus providing definitive diagnoses (van der Waal 2009) and reducing the risk of 'under-diagnosis' inherent in incision biopsy sampling; we have previously reported 'under-diagnosis' of dysplasia in 28%, and masking of invasive cancer in 9%, of treated PMD lesions (Goodson et al 2012).

Whilst a number of authors have reviewed the use of intra-oral CO_2 laser ablative surgery (Chandu & Smith 2005, van der Hem et al 2005, Deppe et al 2012, Brouns et al 2013) or excision surgery (Yang et al 2011, Matsumoto et al 2015) they have actually treated relatively small numbers of leukoplakia patients and have not carried out any comparative analyses of technique efficacy.

Brouns et al (2014) recently described the treatment of 144 patients with oral leukoplakia using surgical excision, laser ablation or via clinical observation alone but did not feel able to compare treatment modalities due to the differing treatment indications. In a direct, retrospective comparison of laser excision and ablation treatment techniques for 77 oral leukoplakic lesions, Del Corso et al (2015) found no significant difference in clinical outcome, although recommended excision of lesions exhibiting dysplasia to prevent recurrence; this study was slightly flawed, however, because although CO_2 laser was used for excision, Nd:YAG was employed for all ablation procedures rendering meaningful comparison difficult.

In Newcastle, we usually only recommend ablation of lesions arising on tightly-bound mucoperiosteal surfaces such as gingiva (previously illustrated in Figure 1.5), alveolar mucosa and hard palate to avoid bony dehiscence, or in soft palate sites to avoid the post-excision risk of oro-nasal fistula formation, and all such lesions must have undergone pre-laser incision biopsy (Thomson 2012c, Thomson & Goodson 2015). Ishi et al (2004) also advised laser excision of PMD lesions on non-keratinised tongue and buccal mucosa, but believed ablation suitable for gingival cases. On occasion, however, ablation may also be a pragmatic solution if small lesions (usually

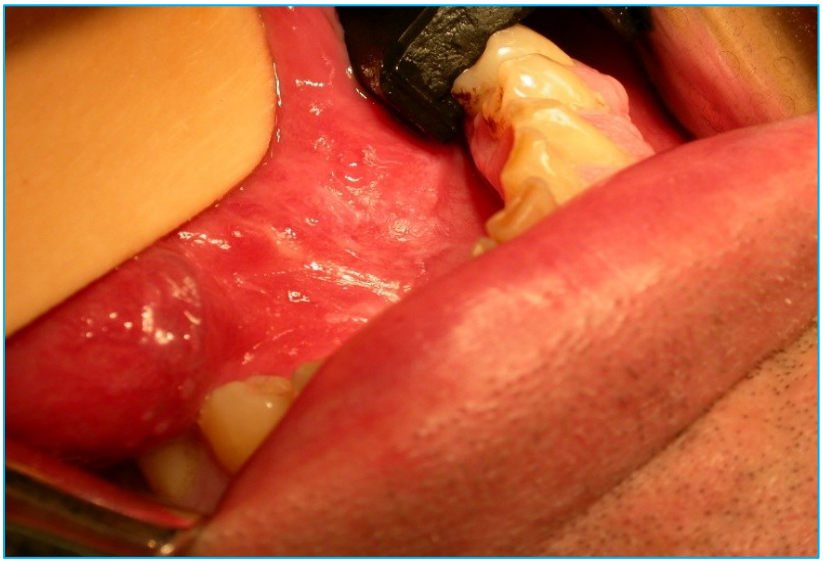
less than 1cm^2 size arising on non-keratinised epithelium) are to be treated, because the resultant thermal artefacts seen in small excision specimens render accurate dysplasia grading unreliable and impractical; this technique, as applied to a suitable floor of mouth lesion is illustrated in Figure 4.7.

(c) Type of Anaesthesia. Figure 4.6 clearly shows an increasing number of LA procedures carried out over time, and interestingly this parallels the similar rise seen in the use of ablative surgery (Figure 4.5). This most likely reflects the increasing personal experience of the operator and more discretionary application of varying laser techniques to different clinical scenarios. Laser ablation is usually a shorter and less technically demanding procedure, which is well tolerated by conscious patients (Thomson 2012c). Not all local anaesthetic procedures are undertaken to facilitate ablation, however, as some patients' general medical status and/or cardio-respiratory co-morbidities inevitably contra-indicate the elective use of general anaesthesia for oral surgery; only 2 patients in the study required intravenous sedation to supplement local anaesthesia.

Laser excision of large dysplastic lesions arising on floor of mouth and ventro-lateral tongue sites can, of course, be technically demanding and may be poorly tolerated by conscious patients. The additional requirements of adjacent soft tissue retraction, haemostasis, accuracy in visualisation of the operative field and lack of patient movement usually necessitate the use of GA techniques, which have been described in detail by the author previously (Thomson 2012c). An example of such a GA laser procedure, a partial glossectomy for lateral tongue dysplasia, was illustrated in Figure 4.2B.

Figure 4.7: Interventional Laser Surgery Ablation (Floor of Mouth) showing (A) localised, small patch of non-homogeneous, mildly dysplastic leukoplakia arising in the left floor of mouth and (B) post-CO_2 laser ablation appearance following superficial mucosal vapourisation without excision.

A



B

(d) Limitations of the Study. Although a large number of CO_2 laser interventions over a 19-year period have been listed and reviewed in this study, the significance of these results are limited by the one-centre basis of the work and particularly by the inevitable clinician bias inherent in treatment selection for these patients. Similarly, this study primarily lists and describes the numbers and types of CO_2 surgical procedures carried out, with little context to explain either the clinical or the histopathological background of treated disease. However, a further contemporaneous examination of the use of laser surgery will be reported in Clinical Study 3, whilst a detailed analysis of clinico-pathological data and patient outcomes following treatment forms the basis of Clinical Study 4 discussed in Chapter 5 of this thesis.

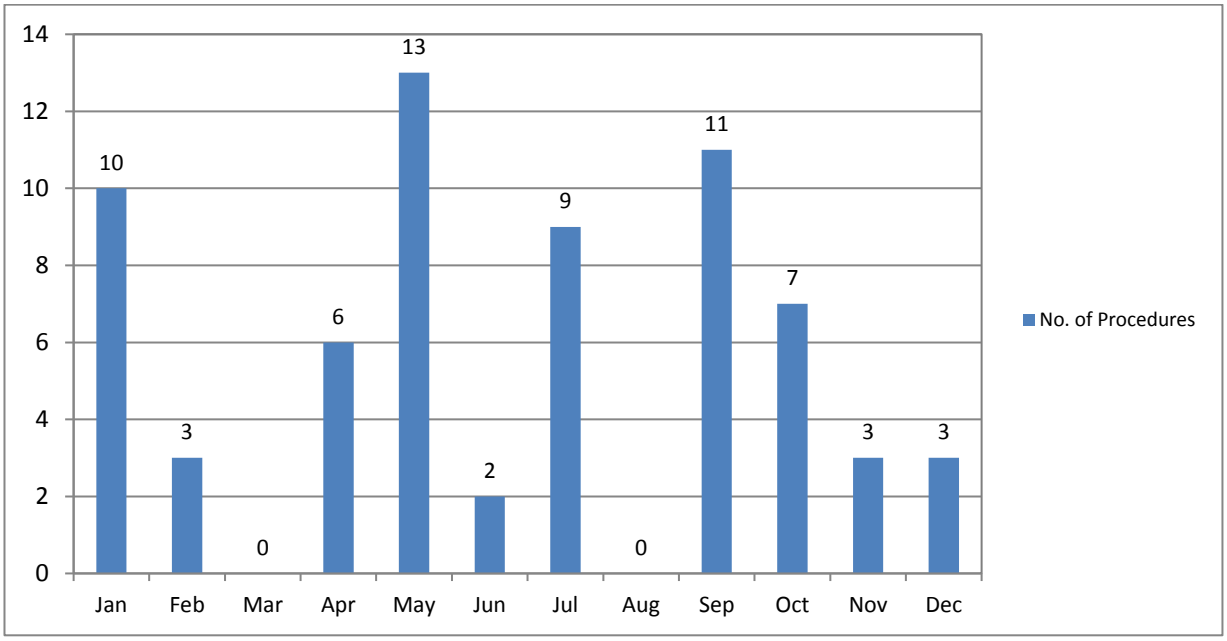
4.3 Clinical Study 3 – A Prospective Study Documenting Interventional CO_2 Laser Surgery Use in Newcastle During 2015

4.3.1. Aims. Directly following on from the previous study, the aim of this further investigation was to prospectively document in greater and additional detail the use of CO_2 laser surgery by the author in the management of oral potentially malignant disease in Newcastle during the 12 months of the calendar year 2015, and to confirm both the pattern of disease presentation and mode of treatment.

4.3.2. Method. In a prospective manner, the author recorded anonymised details of all PMD laser operations carried out during the 12 month period detailing the age and sex of treated patients, their presenting clinical lesions, histopathological diagnoses, length of time between treatment decision and subsequent attendance for laser surgery, the mode of surgical intervention (excision or ablation), and the use of general anaesthesia (GA) or local anaesthesia (LA) techniques.

4.3.3. Results. Full anonymised details of patients operated on by the author and undergoing interventional laser surgery during 2015 are listed in Appendix IV. In total, 67 laser operations were carried out during the 12 months and these are summarized in Figure 4.8 which illustrates the numbers of procedures carried out each month; numbers ranged from 0 to 13 dependent upon both operating theatre timetabling and patient and surgeon availability.

Figure 4.8: Number of Interventional Laser Surgery Procedures Performed Each Month During 2015 (total number of procedures = 67).



(a) Clinico-Pathological Features. 39 male patients (age range 38-84yrs; mean age 59.8yrs) and 28 female patients (age range 37-81yrs; mean age 58.5yrs) were treated during this period. 51 patients were new PMD referrals undergoing laser surgery for the first time, whilst 16 cases attended for repeat laser surgery; none of the 67 patients underwent more than 1 laser surgery procedure during the 12 month study period. The majority of treated PMD lesions appeared clinically as oral leukoplakias (56 or 83.5%), with erythroleukoplakia and erythroplakia much less common, as shown in Table 4.2. Figure 4.9 confirms that most laser-treated lesions presented on floor of

mouth and ventrolateral tongue sites (34 or 50.7%). In terms of histopathological diagnoses, Table 4.3 reveals that 41 lesions (61%) exhibited features of either epithelial dysplasia or carcinoma-in-situ, 13 (19.4%) were diagnosed as proliferative verrucous leukoplakia (PVL), whilst a further 10 (14.9%) showed features of PVL in combination with dysplasia.

TABLE 4.2: CLINICAL APPEARANCE OF TREATED PMD LESIONS

Clinical Appearance	No. of Patients	%
Leukoplakia	56	83.5
Erythroleukoplakia	10	15.0
Erythroplakia	1	1.5
Total	67	100

Figure 4.9: Number of Interventional Laser Surgery Procedures Performed Plotted against Anatomical Site (total number of procedures = 67) where *FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.*

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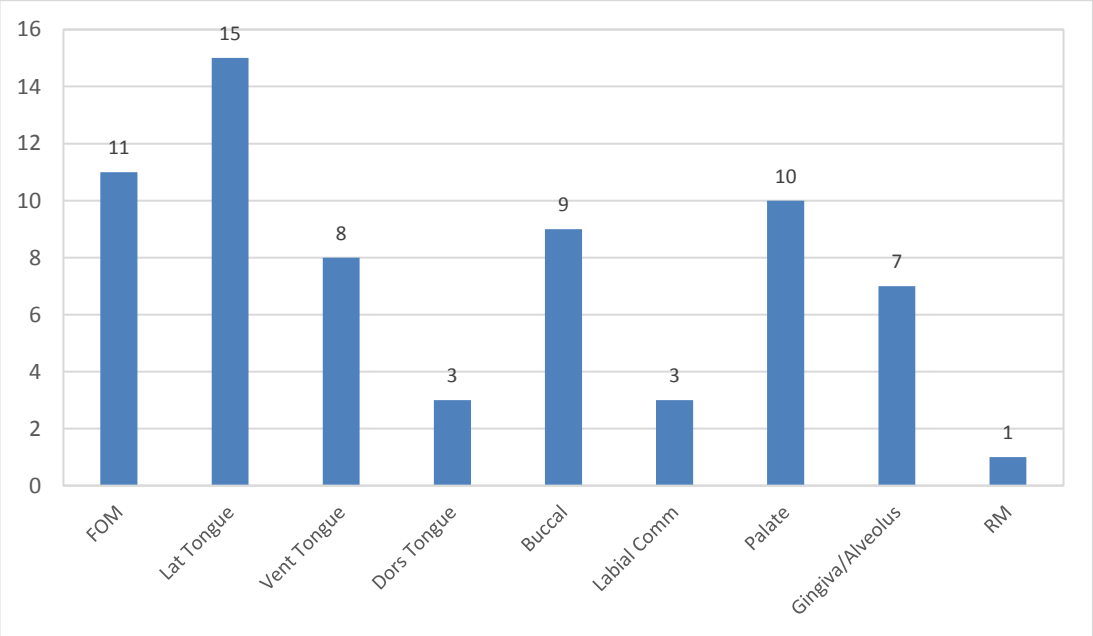


TABLE 4.3: HISTOPATHOLOGY DIAGNOSES FOR TREATED PMD LESIONS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	1	1.5
Chronic Hyperplastic Candidosis (CHC)	2	3.0
Proliferative Verrucous Leukoplakia (PVL)	13	19.4
Mild Dysplasia	24	35.8
Mild Dysplasia + PVL	9	13.4
Moderate Dysplasia	7	10.4
Moderate Dysplasia + PVL	1	1.5
Severe Dysplasia	8	12.0
Carcinoma-in-Situ	2	3.0
Total	67	100.0

(b) Use of Interventional Laser Surgery. Review of the data in Appendix IV reveals that the time to laser treatment, defined as the interval between initial diagnosis and treatment decision to the date when laser surgery was carried out, varied from 2 to 15 weeks, with an overall mean of 8 weeks. In relation to the specific use of CO_2 laser in the 67 cases, most procedures (46) were performed as surgical excision biopsies, with the majority (42) carried out under GA. Table 4.4 confirms that, whilst most laser excision procedures (31) were carried out using GA, ablative surgery was performed in similar numbers under GA and LA; 11 and 10 operations, respectively.

TABLE 4.4: USE OF GENERAL ANAESTHESIA (GA) AND LOCAL ANAESTHESIA (LA) FOR LASER EXCISION AND ABLATION PROCEDURES

	GA	LA	Totals
Laser Excision	31	15	46
Laser Ablation	11	10	21
Totals	42	25	67

Figure 4.10 illustrates the use of GA and LA techniques applied to the varying anatomical sites of treated PMD lesions confirming that, whilst most PMD sites were operated on using either anaesthetic technique, ventrolateral tongue surgery was more often performed under GA (18) compared with LA (5).

Figure 4.10: Number of GA and LA Laser Surgery Procedures Plotted against Anatomical Site (total number of procedures = 67) where *FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.*

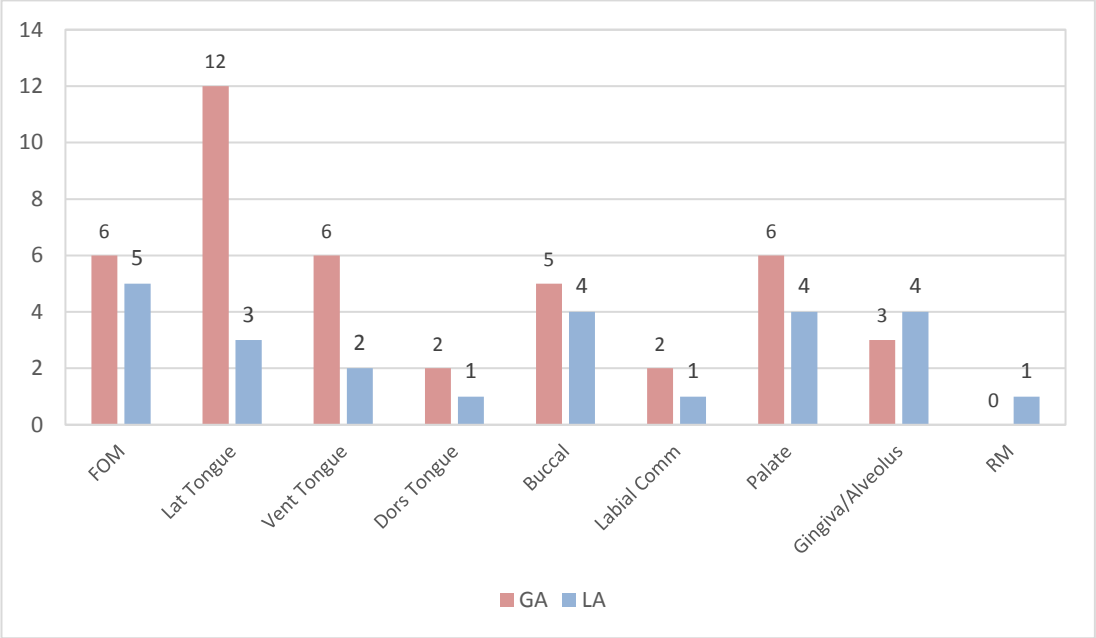
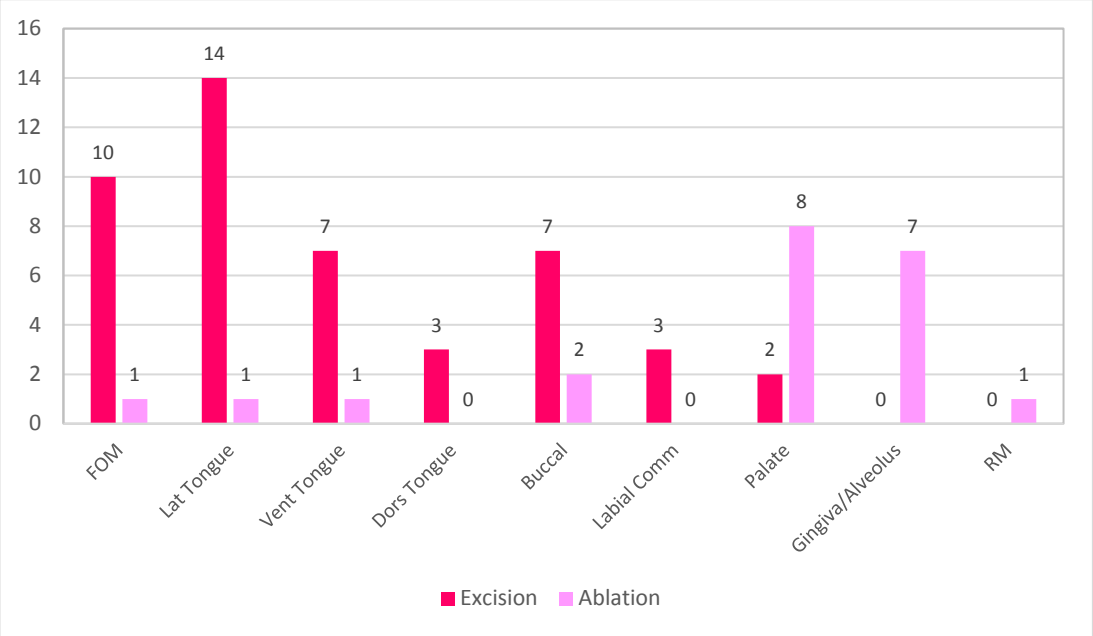


Figure 4.11 similarly plots the number of laser excision or ablation techniques performed at each anatomical site, showing a clear predominance for excision surgery to occur at floor of mouth and ventrolateral tongue sites (31), whilst laser ablation was primarily used for palatal, gingival and alveolar lesions (16).

Figure 4.11: Number of Laser Excision and Ablation Procedures Plotted against Anatomical Site (total number of procedures = 67) where *FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.*



4.3.4. Discussion.

(a) Patient Numbers and Demographics. By carrying out a prospective data collection of CO_2 laser operations, this study has allowed additional characterisation of patients and PMD disease in North-East England over a 12 month period in 2015. Whilst concentrating on patients undergoing intervention, the age and sex profile of these 67 laser patients is very similar to the demographic profile observed in the cross-sectional patient study reported in Chapter 3 with, in addition, the confirmation that the predominant clinical presentation of oral leukoplakia arising at floor of mouth and ventro-lateral tongue sites remains highly consistent between studies.

(b) Clinico-Pathological Features. Unsurprisingly, as a study group undergoing interventional management, the vast majority of PMD lesions were shown to be dysplastic or characterised as exhibiting features of PVL on histopathological examination. It was not, of course, the remit of this study to analyse clinico-pathological data in depth (particularly as this forms an

important part of the investigation in Chapter 5) but nonetheless such observation supports the profiling of PMD patients and histopathology data presented in Chapter 3.

(c) Interventional Laser Surgery. Whilst the previous study reviewed the evolution and overall utilization of CO_2 laser surgery as a treatment modality over a 19-year period, this study was designed to analyse contemporaneous interventional management over a more specific 12 month period. Interestingly, both the numbers of treated patients and the mode of laser treatment remained highly consistent between studies.

It was interesting to note the varying numbers of cases operated upon each month (0 to 13, with a mean of 5.6); these figures were influenced not only by the number of patients presenting for treatment but also the myriad of administrative influences regarding clinic and theatre timetabling and both patient and surgeon availability.

A useful, additional observation in this investigation was the determination of treatment times for patients: 64 patients (95%) were operated on within 12 weeks of diagnosis, whilst 2 patients waiting 14 and 15 weeks for treatment (study numbers L58 and L7, respectively, in Appendix IV) specifically requested a later date for their surgery. Dost et al (2014) reported that a 6 month period may be considered as a pragmatic 'cut-off' to account for biopsy sampling error or the co-existence of unexpected malignancy during PMD assessment. Whilst no specific time frame or guidelines have ever been proposed regarding PMD treatment intervention, a 12 week period seems reasonable to rule out significant disease progression between initial incision biopsy diagnosis and intervention; this is the time frame we have tried to adhere to in our treatment protocols (Thomson & Wylie 2002, Thomson 2012c & 2014).

Diajil et al (2104) previously reviewed 100 Newcastle PMD patients and undertook a comprehensive analysis of clinical management times, confirming that 91% of patients were diagnosed and 49% definitively treated within 12 weeks of initial referral. Any delayed management, however, which primarily affected patients assessed as 'low risk' PMD disease was not found

to adversely influence clinical outcome. Issues related to outcome following PMD treatment will be reviewed in detail in the next chapter of this thesis.

(d) Laser Excision versus Ablation. As previously discussed in Section 4.2.4, CO_2 laser surgery usefully offers both excision and ablative modes of treatment, although laser excision biopsy remains the preferred treatment option for oral PMD lesions, confirmed in this study by its use in 46 patients (69%). The role of laser ablation in the superficial destruction of palatal, gingival and alveolar lesions is supported by Figure 4.11 which confirms that 16 out of 18 lesions at these sites were treated by ablation rather than excision. Many of these issues have already been covered in the previous section of this chapter.

(e) Type of Anaesthesia. Although the majority of laser surgery was carried out under GA (42 cases or 63%), Figure 4.10 shows that both GA and LA techniques were utilised at most oral sites during the study except for lateral and ventral tongue lesions which were primarily operated on under GA (18 out of 23 cases). Decisions regarding treatment choice and the use of GA or LA for individual procedures requires careful assimilation of background medical issues, the specific technical requirements of the operative procedure and consideration of overall patient management issues, as previously discussed in Section 4.2.4.

(f) Limitations of the Study. This is a review of 12 months laser surgery performed by one clinician treating PMD lesions in Newcastle upon Tyne. Similar to the comments in Section 4.2.4, the study is clearly limited by its one-site location, a vulnerability to treatment bias and its descriptive nature, although background clinico-pathological data for the treated patients and their presenting PMD lesions have been expanded upon and further characterised.

4.4 Conclusions

Contemporaneous opinion in the PMD literature now emphasizes the role of interventional management so that definitive surgical excision, rather than clinical monitoring or medical therapy, is most often recommended to treat potentially malignant oral lesions (Gomes & Gomez 2013, Dost et al 2014). It has, of course, been this author's opinion for many years that interventional laser surgery offers a pragmatic and effective therapeutic intervention during oral carcinogenesis, and the unique and substantial data documenting 840 laser surgery operations carried out over a 20-year period, presented and analysed in this chapter, is a clear testimony to this clinical management strategy. In the next chapter of this thesis, however, the efficacy of this treatment intervention will be tested by a detailed review of long-term clinical outcome data for a 590 PMD patient cohort.

Chapter Five

CLINICAL STUDY 4

Clinical, Histopathological & Clinical Outcome Analyses for Newcastle Potentially Malignant Disorder Patients

1996-2014

5.1 Introduction

The protocol for interventional laser surgery adopted by the author in Newcastle (Thomson & Wylie 2002), whereby PMD lesions are provisionally characterised by incision biopsy and subsequently treated by formal laser excision or ablation of 'high risk' dysplastic lesions, has undoubtedly helped rationalize modern management techniques for patients presenting with oral potentially malignant lesions offering both definitive diagnosis through whole lesion analysis and efficacious, low morbidity treatment (Thomson 2012c, Goodson et al 2012, Thomson 2014). It is encouraging that most contemporaneous authors now support such a management strategy (Mehanna et al 2009, van der Waal 2009a, Dost et al 2014).

The specific hypothesis that such intervention prevents or reduces the ultimate risk of malignant transformation remains to be proven, however. Edwards (2014) commented that surgical excision of dysplastic oral lesions might reduce the risk of malignancy by 50%, but this is only an estimate and not readily applicable as a statistic during the active treatment of individual patients or lesions.

The absence of relevant randomised clinical trials, especially comparing the benefits of surgical intervention with clinical observation or lesion surveillance, weakens the evidence base. It remains difficult, however, to envisage a comprehensive trial design which has both scientific validity and acceptability to clinicians and patients; a 'non-intervention' arm to manage lesions exhibiting significant dysplastic change, for example, being especially problematic.

As documented in Chapter 1, we have undertaken and published a number of Newcastle patient cohort studies but these have been based upon relatively small patient numbers and varying follow-up periods. In the absence of meaningful clinical trial data, further detailed analysis of a large patient cohort with well-defined potentially malignant disease undergoing a coordinated treatment and follow-up regime seemed pertinent.

5.2 Aim of the Study

The aim of this retrospective, cohort study was thus to collate and then review in detail all available patient demographic, clinico-pathological, diagnostic, treatment and clinical outcome data for patients that attended the Newcastle Oral and Maxillofacial Surgery service for CO_2 laser treatment of new-onset oral potentially malignant disease between 1st August 1996, when the author commenced consultant practice and established dedicated potentially malignant disorder services, and a clinical outcome census date of 31 December 2014.

5.3 Method

5.3.1. Caldicott Approval. As previously documented in Chapter 2, Caldicott approval was obtained from the Joint Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust to facilitate anonymized data collection from medical records, operating logs and pathology reports from potentially malignant disorder patients treated by the author and attending specialist Oral and Maxillofacial services at Newcastle Dental and Royal Victoria Infirmary hospitals (Appendix I). Ethical advice was sought and confirmed that individual patient consent was not required for anonymized, retrospective clinico-pathological and treatment data collection and analysis.

5.3.2. Patient and Treatment Details. Utilising theatre log books as the starting point for data collection, supplemented when available by patients' clinical records and pathology reports, anonymized demographic and clinico-pathological details were recorded for individual patients undergoing CO_2 laser surgery treatment for oral potentially malignant disorders between August 1996 and December 2014 (inclusive). As the author held personal clinical responsibility for these patients, it was felt data collection would be accurate and that few patients, if any, would be missed from the collection process.

The following data was documented for each study case: date of initial treatment by CO_2 laser surgery (facilitating individual patient study numbers), patient age and sex, clinical appearance (leukoplakia, erythroleukoplakia or erythroplakia) and anatomical site of treated oral mucosal lesions, original histopathology diagnoses for both incision and where appropriate post-laser excision biopsies, together with details of follow-up and the need for further laser treatment (distinguishing single from multiple procedure cases). Whilst the total number of follow-up appointments was not recorded for each individual, additional interventional treatment episodes were all re-documented as above, and a formal clinical outcome status (described in detail in Section 5.3.4) was determined for each individual at the time of the study census date of 31 December 2014.

Inclusion criteria for the study required that all clinical presentations of PMD disease had been new, with untreated oral mucosal lesions confirmed on provisional, incision biopsy diagnosis to be classifiable as an oral potentially malignant disorder (as listed in Table 1.2), and with follow-up and clinical outcome data fully documented up to 31 December 2014. Specifically excluded were patients with a previous history of oral cancer or pre-cancer, those presenting with widespread multi-focal potentially malignant disease, and patients who had previously undergone radiotherapy treatment for a head and neck malignancy.

5.3.3. Histopathology Diagnoses. All incision biopsy procedures were carried out in Oral and Maxillofacial Surgery clinics under the personal direction of the author and laser excision specimens were obtained following interventional laser treatment as documented in previous Chapters; all laser surgery was carried out by the author, or by clinical colleagues working under direct supervision of the author, within 6 to 12 weeks following incision biopsy to avoid diagnostic confusion through potential disease progression. Formalin-fixed tissue specimens were assessed via standardized histopathology examination by experienced oral pathologists at the Royal Victoria Infirmary working to agreed diagnostic criteria with appropriate peer review and consensus grading (Sloan 2012). Using the World Health Organization (WHO) classification, specimens were graded into mild,

moderate or severe dysplasia categories, carcinoma-in-situ (CiS) or squamous cell carcinoma (SCC); Gale et al (2005). In addition, the presence of hyperkeratosis, lichenoid inflammation (LI), or the diagnoses of proliferative verrucous leukoplakia (PVL) or chronic hyperplastic candidosis (CHC) were recorded. All histopathology diagnoses were based on the original reports produced by the pathologists at the time of tissue analysis, and no formal review or re-interpretation of specimens was attempted.

5.3.4. Clinical Outcome Categories. Review of all available patient clinical records was carried out by the author and each study patient was assigned to one of the following, specific clinical outcome categories, modified from the outcome categories reported in Table 1.5, and defined as of 31 December 2014 as: Disease Free (DF), the absence of clinical signs of potentially malignant disease, Further Disease which ultimately progressed to Disease Free status following further intervention (Further/Disease Free), Further Disease which persisted despite intervention (Further/Persistent Disease) and Malignant Transformation (MT), in which the presence of invasive oral squamous cell carcinoma was confirmed by histopathological examination.

5.3.5. Statistical Analyses. A variety of statistical techniques were employed to analyse the study results:

(a) Descriptive Statistics were used throughout to both order and summarise details of patient demography, clinical features and pathological diagnoses from the study population, together with documentation of treatment interventions and overall clinical outcome and follow-up data.

(b) Histopathology diagnoses were primarily treated as categorical variables, and specific testing of agreement between initial incision biopsy diagnoses and post-laser excision biopsy diagnoses carried out using 4 defined histopathology categories: Epithelial Dysplasia, Squamous Cell Carcinoma (SCC), together with the identifiable presence of Lichenoid inflammation (LI) or Proliferative Verrucous Leukoplakia (PVL) in biopsy specimens. Diagnoses of carcinoma-in-situ (CiS) were combined with Severe Dysplasia and micro-invasive carcinoma was included with Squamous Cell Carcinoma.

The percentage overall agreement was determined for each histopathology category as well as overall agreement when considering all 4 categories together. Kappa and weighted kappa statistics were used to measure the degree of agreement between incision biopsy and post-laser excision biopsy within each of the histopathology categories. A kappa coefficient of 1 was taken to represent perfect agreement, whilst less than 1 was considered less than perfect agreement.

For histopathology categories assessable as either positive or negative, such as the identification of squamous cell carcinoma, the presence of lichenoid inflammation or features of proliferative verrucous leukoplakia, the sensitivity and specificity of initial, incision biopsies was determined. Sensitivity demonstrated how often the incision biopsy was positive when confirmed by a positive result on post-laser excision biopsy. Specificity showed how often the incision biopsy was negative when the condition proved negative on post-laser biopsy. Patients with incision and excision biopsies from more than one treatment episode were treated independently in the analysis, under the assumption that biopsy agreement was no more or less likely within individual patients (for samples taken at different time points) compared with those between different patients.

(c) Clinical Outcome data were first stratified for statistical analysis as either a Successful Outcome (Disease Free) or Failure (Further PMD disease or Malignant Transformation); success rates and 95% Confidence Intervals (CI) were calculated. Multivariate logistic regression was used to analyse factors potentially prognostic of a Disease Free outcome (including age at first treatment, sex of patient, clinical lesion appearance, anatomical site of first presentation and initial, incision biopsy histopathology). Relationships between the potential factors were explored using chi-square tests, correlation coefficients or logistic regression to check for collinearity. The factors were first explored univariately and then a multivariate model was built using a stepwise procedure until all variables were significant at the 10% level. Candidate variables for the initial model were those significant at the 20% level univariately. If collinearity was suspected only the most significant univariate relationships were included in the model.

(d) Further comparative analyses between the defined Clinical Outcome categories of Disease Free, Further/Disease Free, Further/Persistent Disease and Malignant Transformation were carried out using, as appropriate, chi-square testing, Fisher's exact test, t-test and Wilcoxon Rank Sum testing, dependent upon the parametric nature of the data and sample size.

(e) Malignant Transformation, essentially the recognition of PMD lesions which progressed to cancer development despite treatment intervention, was further analysed using a univariate Cox regression model to investigate the clinico-pathological variables that might influence time to malignant transformation. Kaplan-Meier survival analyses were also carried out, as appropriate, for these variables.

All statistical analyses were done using SAS/STAT® 9.3 software (SAS Institute Inc, Cary, USA).

5.4 Results

5.4.1. Patient Demography. A total of 590 PMD patients meeting the study criteria were treated during the 19-year period, and their full demographic, clinico-pathological, treatment and outcome data are listed in database format in Appendix V. All interventional treatment details were recorded as appropriate for each patient up until the census date of 31 December 2014, unless malignant transformation supervened in which case this was regarded as the individual's exit-point from the study.

Review of the database shows that patients requiring single treatment interventions were summarized as one-line entries, whilst patients undergoing multiple treatments had each intervention and corresponding clinico-pathological data recorded on subsequent entry lines.

The clinical outcome categories may be exampled by the following study patients:

(a) Disease Free status (DF) is illustrated by Study Number 1998/2 which summarizes a patient successfully treated by laser excision of a severely dysplastic ventral tongue lesion in January 1998 with no subsequent episodes of PMD disease or malignant transformation,

(b) Further/Disease Free outcome is shown in Study Number 1998/12 in which the patient underwent 2 treatment interventions, in November 1998 and June 2005 for dysplastic buccal lesions, ultimately determined as disease free by the time of study census date,

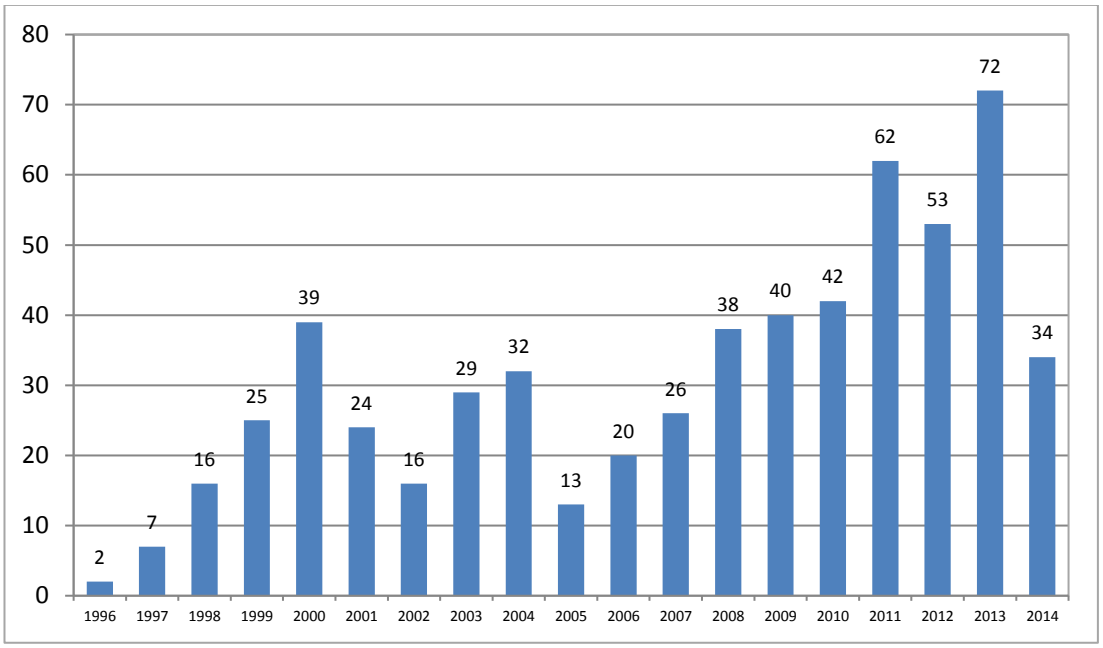
(c) Further/Persistent Disease is exampled by the history summarised in Study Number 2000/12 in which, despite laser ablation of a moderately dysplastic alveolar lesion in March 2000, the patient was noted to exhibit persistent PMD disease at the census date,

(d) Malignant Transformation (MT) is illustrated firstly by Study Number 1996/1, in which 8 treatment interventions at multiple oral sites were carried out over a 17-year period until malignancy was diagnosed in July 2013, and secondly by Study Number 1998/1 in which an unexpected micro-invasive squamous carcinoma was identified upon histopathological examination of a lateral tongue laser excision specimen in January 1998.

In relation to patient age, the mean age at presentation was 59.7 years (Standard Deviation 12.6), with a median of 60 years (age range 23 to 94 years). 347 patients (59%) were male and 243 (41%) female. In relation to reported risk factor behaviours, 513 patients (87%) were current or ex-smokers, whilst 496 (84%) regularly consumed alcohol.

Overall patient distribution throughout the study period, recorded against their year of first presentation, is illustrated in Figure 5.1.

Figure 5.1: PMD Patient Presentation showing the numbers of new patients who presented for treatment each year between 1996 and 2014.



5.4.2. Clinical Features. Table 5.1 summarises the clinical appearance for all 590 PMD lesions and shows that the vast majority (468 or 79%) presented as leukoplakias, with erythroleukoplakia and, especially, erythroplakia much less common; 17% and 4%, respectively. Table 5.2 lists the anatomical site distribution for these lesions, confirming that floor of mouth and ventrolateral tongue sites were most frequently affected (in 358 cases or 61%), with buccal mucosa the next most common site (59 cases or 10%).

TABLE 5.1: CLINICAL APPEARANCE OF ALL PMD LESIONS

Clinical Appearance	No. of Patients	%
Leukoplakia	468	79
Erythroleukoplakia	99	17
Erythroplakia	23	4
Total	590	100

TABLE 5.2: ANATOMICAL SITE DISTRIBUTION OF ALL PMD LESIONS

Anatomical Site	No. of Patients	%
Floor of Mouth	172	29.2
Lateral Tongue	130	22.0
Buccal Mucosa	59	10.0
Palate	57	9.7
Ventral Tongue	56	9.5
Labial Commissure	29	4.9
Gingiva	21	3.6
Fauces	20	3.4
Alveolus	18	3.1
Labial Mucosa	11	1.9
Dorsum of Tongue	11	1.9
Fauces/Retromolar	3	0.5
Retromolar	3	0.5
Totals	590	100.0

5.4.3. Histopathology Features.

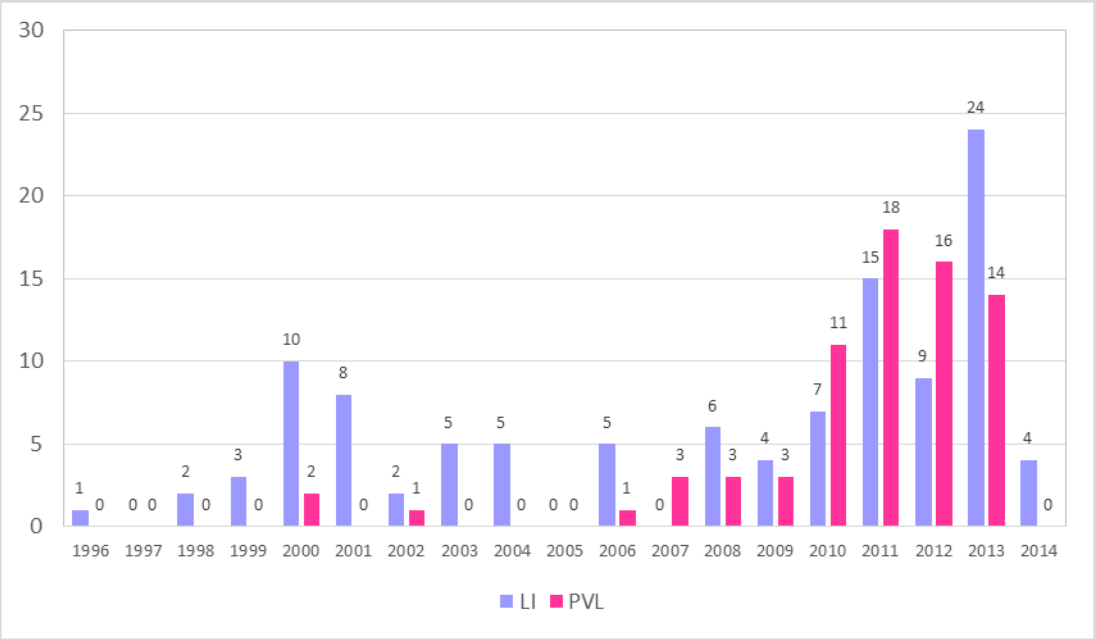
(a) Descriptive Analysis. An overall histopathological grading for each of the 590 cases was obtained for initial profiling, based upon the most significant or severe diagnosis recorded from either incision and/or laser excision biopsy specimen data; these are listed in Table 5.3. 522 cases (88.5%) were shown to exhibit dysplastic change or the presence of carcinoma-in-situ. Features of lichenoid inflammation (LI) were seen in 88 cases, with the majority 60 (68.2%) also showing dysplasia. Proliferative Verrucous Leukoplakia (PVL) was reported in 74 cases, with the majority 59 (79.7%) again associated with dysplasia of varying grade.

TABLE 5.3: HISTOPATHOLOGY DIAGNOSES FOR ALL PMD LESIONS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	8	1.4
Hyperkeratosis + Lichenoid Inflammation (LI)	28	4.8
Chronic Hyperplastic Candidosis (CHC)	17	2.9
Proliferative Verrucous Leukoplakia (PVL)	15	2.5
Mild Dysplasia	118	20.0
Mild Dysplasia + LI	28	4.7
Mild Dysplasia + PVL	40	6.8
Moderate Dysplasia	105	17.8
Moderate Dysplasia + LI	24	4.0
Moderate Dysplasia + PVL	15	2.5
Severe Dysplasia	99	16.8
Severe Dysplasia + LI	8	1.4
Severe Dysplasia + PVL	4	0.7
Carcinoma-in-Situ	81	13.7
Total	590	100.0

Whilst all the diagnostic categories were seen fairly consistently throughout the 19 year study period (as fully listed in Appendix V), Figure 5.2 illustrates that a specific, increasing trend was seen for lichenoid inflammation (LI) and especially proliferative verrucous leukoplakia (PVL) to be identified more frequently upon histopathological examination of biopsy specimens from 2010 onwards.

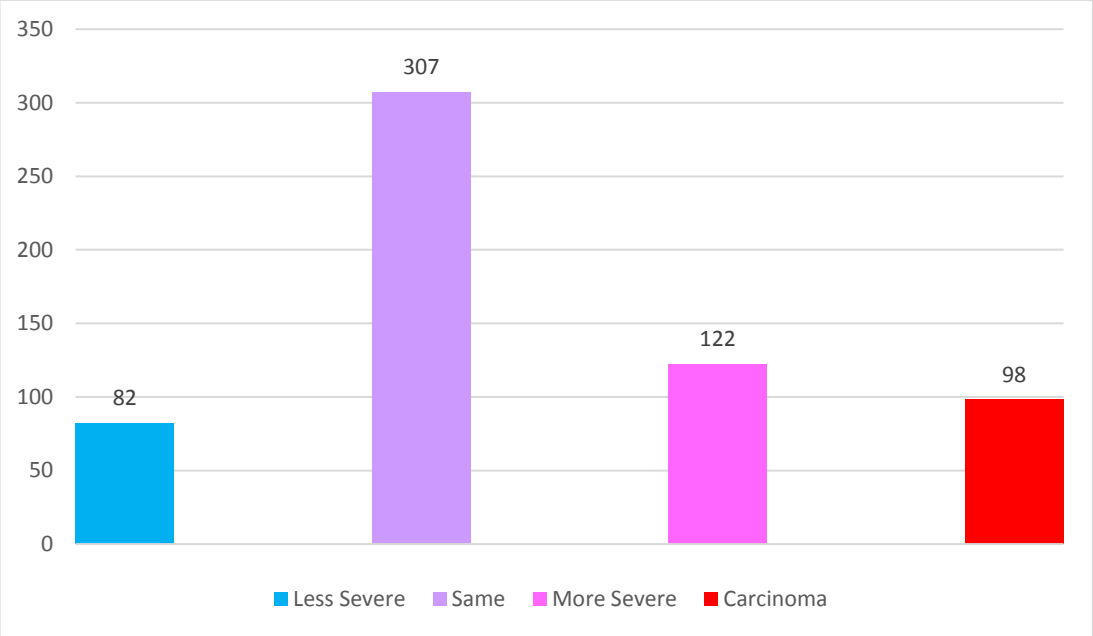
Figure 5.2: Change in Incidence of Histopathological Diagnoses of Lichenoid Inflammation (LI) and Proliferative Verrucous Leukoplakia (PVL) over Time (No. of Diagnoses between 1996 and 2014).



There were relatively few cases exhibiting only simple hyperkeratosis on biopsy (1.4%) which presented as leukoplakias at a variety of intra-oral sites. In relation to chronic hyperplastic candidosis (diagnosed in 2.9% of cases), the majority were leukoplakic lesions arising on the labial commissures; all original data for these categories can be accessed in Appendix V.

(b) Agreement Between Incision and Excision Biopsy Diagnoses. Both initial, incision biopsy histopathology diagnoses and post-laser excision specimen histopathology diagnoses were available for direct comparison in 609 treatment interventions. These results are graphically represented in Figure 5.3 which confirms that in 307 cases (50%) biopsy diagnoses were seen to agree, whereas in 220 (36%) excision specimens had to be effectively 'up-graded' as they showed more severe dysplastic change or even invasive carcinoma, compared with their incision biopsy counterparts. Only in 82 cases (14%) did the laser excision specimen exhibit less severe histopathological changes than those seen on incision biopsy.

Figure 5.3: Direct Comparison of Laser Excision Histopathology Diagnoses with Initial Incision Biopsy Data stratifying results into Less Severe, Same, and More Severe Dysplasia categories or Identification of Carcinoma (number of cases = 609).



Statistical analysis of agreement between incision and excision biopsy diagnoses was first carried out using the histopathological categories of 'no dysplasia' or the presence of 'mild, moderate and severe dysplasia', as summarised in Table 5.4. Overall agreement occurred in 362 out of 609 samples (59.4%). Weighted kappa was 0.45 (95% confidence interval 0.40 to 0.51) indicating moderate agreement.

TABLE 5.4: AGREEMENT ON DYSPLASIA DIAGNOSES BETWEEN INCISION AND EXCISION BIOPSIES

(MEASURED AS NO DYSPLASIA or MILD, MODERATE and SEVERE)

Table of Dysplasia by Post-Laser Excision Dysplasia					
Dysplasia(Incision Biopsy)	**Dysplasia (Laser Excision)**				
Frequency **Percent** **Row Percent** **Column Percent**	**No**	**Mild**	**Moderate**	**Severe**	**Total**
No	131	30	9	12	182
	21.51	4.93	1.48	1.97	29.89
	71.98	16.48	4.95	6.59	
	58.74	17.86	7.14	13.04	
Mild	26	116	33	4	179
	4.27	19.05	5.42	0.66	29.39
	14.53	64.80	18.44	2.23	
	11.66	69.05	26.19	4.35	
Moderate	24	17	69	30	140
	3.94	2.79	11.33	4.93	22.99
	17.14	12.14	49.29	21.43	
	10.76	10.12	54.76	32.61	
Severe	42	5	15	46	108
	6.90	0.82	2.46	7.55	17.73
	38.89	4.63	13.89	42.59	
	18.83	2.98	11.90	50.00	
Total	223	168	126	92	609
	36.62	27.59	20.69	15.11	100.00

Although formal histopathological re-grading by oral pathologists to establish a binary assessment (such as proposed by Kujan et al 2006) was not carried out in this study, a further agreement analysis between incision and excision diagnoses was performed by arbitrarily combining mild and moderate categories together as ‘low grade’ dysplasia whilst severe was considered ‘high grade’ dysplasia; these data are shown in Table 5.5. Overall agreement was seen in 412 out of 609 samples (67.7%). Weighted kappa was 0.43 (95% confidence interval 0.36 to 0.49) again indicating moderate agreement between samples.

TABLE 5.5: AGREEMENT ON DYSPLASIA DIAGNOSES BETWEEN INCISION AND EXCISION BIOPSIES

(MEASURED AS NO DYSPLASIA or 'LOW GRADE' and 'HIGH GRADE')

Table of Dysplasia by Post-Laser Excision Dysplasia				
Dysplasia (Incision Biopsy)	**Dysplasia (Laser Excision)**			
Frequency **Percent** **Row Percent** **Column Percent**	**No**	**'Low Grade' (Mild/Moderate)**	**'High Grade' (Severe)**	**Total**
No	131	39	12	182
	21.51	6.40	1.97	29.89
	71.98	21.43	6.59	
	58.74	13.27	13.04	
'Low Grade' (Mild/Moderate)	50	235	34	319
	8.21	38.59	5.58	52.38
	15.67	73.67	10.66	
	22.42	79.93	36.96	
'High Grade' (Severe)	42	20	46	108
	6.90	3.28	7.55	17.73
	38.89	18.52	42.59	
	18.83	6.80	50.00	
Total	223	294	92	609
	36.62	48.28	15.11	100.00

In addition, the presence or absence of lichenoid inflammation (LI) observed in incision and excision biopsies was compared, and summarised in Table 5.6. Overall agreement occurred in 531 out of 609 samples (87.2%). The sensitivity of the initial, incision biopsy was 55.7% and the specificity 91.3%. Kappa was 0.43 (95% confidence interval 0.32 to 0.53) indicating moderate agreement. Similarly, in Table 5.7, the histopathological identification of proliferative verrucous leukoplakia (PVL) was compared between incision and post-laser excision specimens. Overall agreement was seen in 567 out of 609 samples (93.1%). The sensitivity of the incision biopsy was 57.4% and the specificity 96.6%. Kappa was 0.56 (95% confidence interval 0.44 to 0.68) indicating moderate agreement.

TABLE 5.6: AGREEMENT ON THE PRESENCE OR ABSENCE OF LICHENOID INFLAMMATION (LI) BETWEEN INCISION AND EXCISION BIOPSIES

Table of LI by Post-Laser Excision LI			
Incision Biopsy LI	**Post-Laser Excision LI**		
Frequency **Percent** **Row Percent** **Column Percent**	**No**	**Yes**	**Total**
No	492 80.79 94.07 91.28	31 5.09 5.93 44.29	523 85.88
Yes	47 7.72 54.65 8.72	39 6.40 45.35 55.71	86 14.12
Total	539 88.51	70 11.49	609 100.00

TABLE 5.7: AGREEMENT ON THE PRESENCE OR ABSENCE OF PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL) BETWEEN INCISION AND EXCISION BIOPSIES

Table of PVL by Post-Laser Excision PVL			
Incision Biopsy PVL	**Post-Laser Excision PVL**		
Frequency **Percent** **Row Percent** **Column Percent**	**No**	**Yes**	**Total**
No	536 88.01 95.89 96.58	23 3.78 4.11 42.59	559 91.79
Yes	19 3.12 38.00 3.42	31 5.09 62.00 57.41	50 8.21
Total	555 91.13	54 8.87	609 100.00

Review of the agreement between incision and excision tissue specimens for the 98 cases in which squamous cell carcinoma (SCC) was identified following laser excision is summarized in Table 5.8. Overall agreement between diagnoses occurred in 527 out of 609 samples (86.5%). The sensitivity of the incision biopsy was 16.3% and the specificity 100%. Kappa was determined as 0.25 (95% confidence interval 0.15 to 0.35) indicating only fair agreement between the two diagnostic samples in this analysis.

TABLE 5.8: AGREEMENT ON THE PRESENCE OR ABSENCE OF SQUAMOUS CELL CARCINOMA (SCC) BETWEEN INCISION AND EXCISION BIOPSIES

Table of SCC by Post-Laser Excision SCC			
Incision Biopsy SCC	**Post-Laser Excision SCC**		
Frequency **Percent** **Row Percent** **Column Percent**	**No**	**Yes**	**Total**
No	511 83.91 86.17 100.00	82 13.46 13.83 83.67	593 97.37
Yes	0 0.00 0.00 0.00	16 2.63 100.00 16.33	16 2.63
Total	511 83.91	98 16.09	609 100.00

In Table 5.9, overall agreement for all histopathological diagnoses between incision and excision specimens is demonstrated, in (A) using the categories: ‘no dysplasia’, or mild, moderate and severe, and in (B) arbitrarily combining mild and moderate as ‘low grade’ and severe as ‘high grade’. There appears slightly more agreement between incision and excision biopsies when the binary system (‘low’ versus ‘high’ grade) is used in the data analysis to categorise dysplasia.

TABLE 5.9: AGREEMENT IN ALL HISTOPATHOLOGY DIAGNOSES BETWEEN INCISION AND EXCISION BIOPSIES INCLUDING:

(A) DYSPLASIA GRADED AS NONE, MILD, MODERATE OR SEVERE

Agree	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	336	55.17	336	55.17
Yes	273	44.83	609	100.00

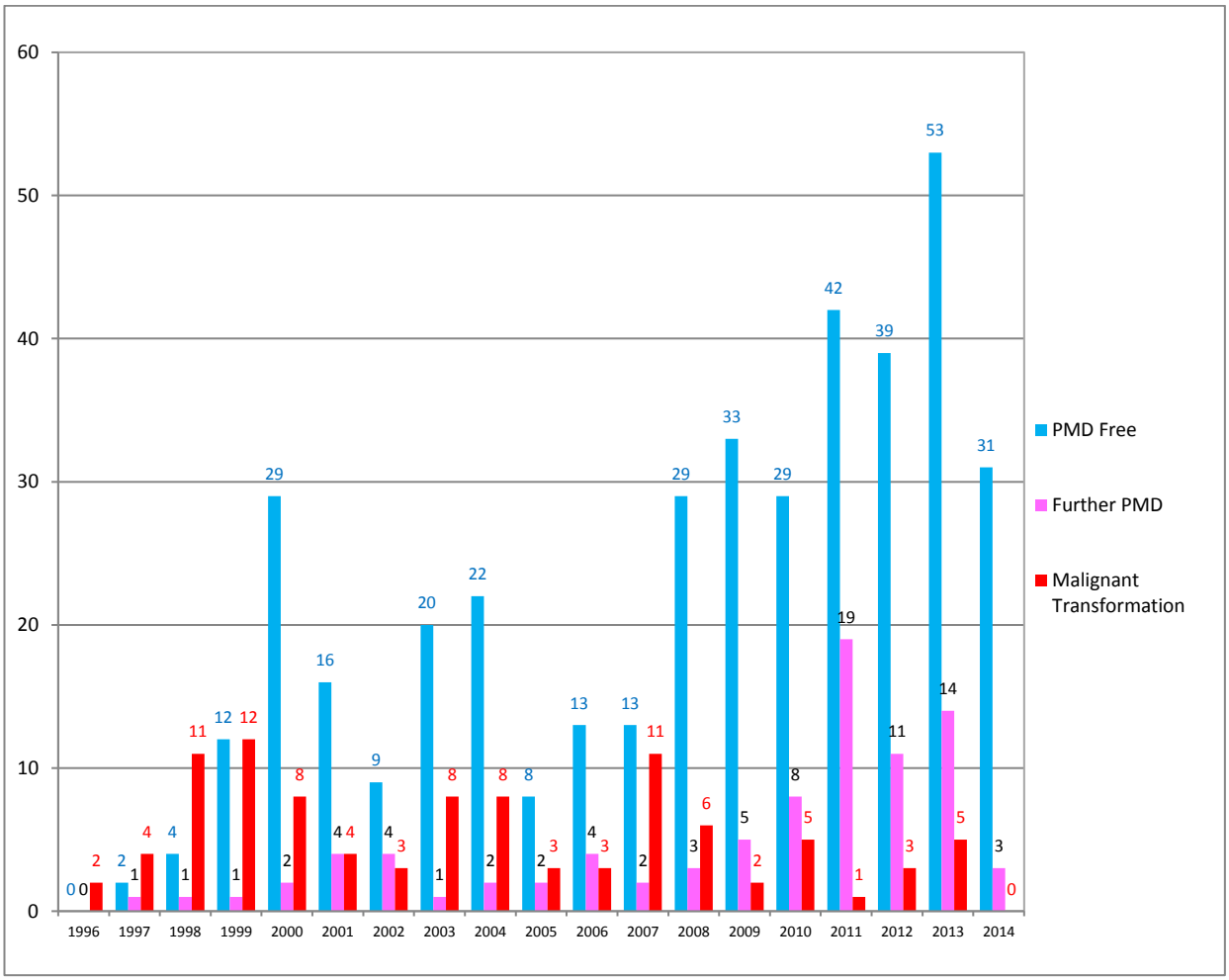
(B) DYSPLASIA GRADED AS NONE or 'LOW GRADE' and 'HIGH GRADE')

Agree	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	296	48.60	296	48.60
Yes	313	51.40	609	100.00

5.4.4. Patient Management. The initial treatment modality was laser excision in 526 patients (89%), and laser ablation in 64 (11%). In total, 773 treatment episodes were carried out on this 590 patient group during the study period, with 609 laser excision specimens obtained for histopathological examination. The mean number of treatments per patient was 1.2 (Standard Deviation 0.6), with a median of 1 (range 1 to 8).

5.4.5. Overall Clinical Outcome. The mean duration of patient follow-up during this study was 7.3 years (Standard Deviation 5.1 years), with a median of 6 years (range 0 to 19 years). Figure 5.4 plots clinical outcome, defined in terms of disease free, further PMD disease or malignant transformation, for patients presenting in each of the study years.

Figure 5.4: Clinical Outcome Data illustrating numbers of patients PMD Disease Free, those exhibiting Further PMD Disease and those undergoing Malignant Transformation each year during the study period.



In terms of overall clinical outcome, Table 5.10 shows that 438 patients (74.2%, with a 95% confidence interval of 70.7 to 77.8%) had a successful outcome and were free from PMD disease at the time of study census date; 404 patients achieved this status immediately following initial laser surgery, whilst an additional 34 became disease free after further laser intervention. These outcomes provided an important distinction and sub-classification, therefore, between 'immediately' disease free cases and those with further disease who only became disease free following additional treatment. Out of the initial 87 patients who required repeat treatment intervention, 53 ultimately showed persistent potentially malignant disease at the time of study census.

TABLE 5.10: OVERALL CLINICAL OUTCOME AT CENSUS DATE (31.12.14)

Clinical Outcome	No. of Patients	%
PMD Disease Free	438	74.2
Further PMD Disease	53	9.0
Malignant Transformation	99	16.8
Total	590	100

Malignant transformation, the development of invasive squamous cell carcinoma and therefore the most significant clinical outcome, was seen in 99 cases, with 80 patients developing a carcinoma at the same oral site as their PMD precursor lesion and 19 at new, distinct oral sites. In 71 cases, the diagnosis of malignancy was made unexpectedly following histopathological examination of initial laser excision specimens, whilst a further 28 patients developed malignancy during clinical follow-up although the time to malignancy varied substantially between 3 months to 17 years post intervention.

In the next sections of this thesis, the specific clinical outcome categories of Disease Free (DF), Further/Disease Free, Further/Persistent Disease and Malignant Transformation will be reviewed and their clinico-pathological features analysed in detail.

5.4.6 Disease Free Patients. In the study, 404 patients (68%) were rendered free from disease following first interventional laser treatment. The clinical appearance of the initial presenting PMD lesions in this patient group is shown in Table 5.11. Although the distribution is similar to that seen in Table 5.1 (which lists the appearance for all 590 lesions), there is a tendency for a higher percentage of leukoplakias and a slightly lower percentage of erythroleukoplakias to be seen in the disease free patient group. Anatomical site distribution for the Disease Free cases mirrored that seen for all 590 PMD lesions summarized in Table 5.2 with no major differences; the most common sites were again the floor of mouth and ventrolateral tongue in 261 cases (64.6%) and buccal mucosa in 32 (8%); original data for this patient group are all listed in Appendix V.

Histopathological diagnoses for these 404 Disease Free cases are shown in Table 5.12, and may be directly compared with data for the 590 lesions in Table 5.3; there would appear to be little difference in the percentage distribution for individual pathology categories, with the majority (359 or 88.9%) again showing features of either dysplasia or carcinoma-in-situ on biopsy.

Associations between clinico-pathological features were checked using chi-square tests for categorical variables or logistic regression for continuous variables (Table 5.13a). Univariate logistic regression analyses of clinico-pathological features potentially influencing disease free status were carried out using initial, incision biopsy diagnoses and these results are shown in Table 5.13b. Multivariate analysis was then performed after excluding lesion site from the model, due to the large number of site categories and their high correlation with other variables, and also excluding PVL identification in incision biopsy specimens as this did not relate univariately. All other variables were included as they reached the 0.2 level of significance on univariate analysis. Sex was subsequently found to be non-significant in the model ($p=0.42$) and was eliminated. All other variables remained significant at the 10% level (although age was considered borderline) and were retained in the model; these results are presented in Table 5.14.

TABLE 5.11: CLINICAL APPEARANCE OF PMD LESIONS IN DISEASE FREE PATIENTS

Clinical Appearance	No. of Patients	%
Leukoplakia	341	85
Erythroleukoplakia	50	12
Erythroplakia	13	3
Total	404	100

TABLE 5.12: HISTOPATHOLOGY DIAGNOSES OF PMD LESIONS IN DISEASE FREE PATIENTS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	5	1.2
Hyperkeratosis + Lichenoid Inflammation (LI)	20	5.0
Chronic Hyperplastic Candidosis (CHC)	14	3.5
Proliferative Verrucous Leukoplakia (PVL)	6	1.5
Mild Dysplasia	94	23.3
Mild Dysplasia + LI	23	5.7
Mild Dysplasia + PVL	29	7.2
Moderate Dysplasia	81	20.0
Moderate Dysplasia + LI	17	4.2
Moderate Dysplasia + PVL	11	2.7
Severe Dysplasia	51	12.6
Severe Dysplasia + LI	6	1.5
Severe Dysplasia + PVL	4	1.0
Carcinoma-in-Situ	43	10.6
Total	404	100.0

TABLE 5.13: ANALYSIS OF CLINICO-PATHOLOGICAL FACTORS INFLUENCING DISEASE FREE STATUS SHOWING (A) RELATIONSHIP BETWEEN FACTORS AND (B) UNIVARIATE ANALYSIS *(BASED UPON FIRST PRESENTATION & INCISION BIOPSY DATA)*

A

	Site	Age	Sex	Lesion	Dysplasia	LI	PVL
Site	-	<0.0001	<0.0001	<0.0001	<0.0001	0.0007	<0.0001
Age		-	0.0654	0.1802	0.0085	0.0064	0.1154
Sex			-	0.0219	0.0219	0.007	0.0903
Lesion				-	<0.0001	0.2756	0.0002
Dysplasia					-	0.0003	0.0004
LI						-	0.0011
PVL							-

p-values from chi-square tests for categorical variables or logistic regression for continuous variables

B

Factor	**Univariate Logistic p-value**
Site	0.0009
Age	0.0255
Sex	0.1124
Lesion	0.0001
Dysplasia (None, Mild, Moderate vs Severe)	<0.0001
LI	0.0428
PVL	0.2887

TABLE 5.14: FINAL MULTIVARIATE MODEL OF CLINICO-PATHOLOGICAL INFLUENCE ON DISEASE FREE STATUS SHOWING ODDS RATIO ESTIMATES AND P-VALUES *(BASED UPON FIRST PRESENTATION & INCISION BIOPSY DATA)*

Effect		**Point Estimate**	**95% Wald Confidence Limits**		**P-value**
Age		0.987	0.971	1.003	0.11
Lesion	**EK vs LK**	0.652	0.266	1.595	0.030
Lesion	**ELK vs LK**	0.525	0.323	*0.854**	
Dysplasia	**Mild vs Severe**	3.010	1.658	*5.464**	0.0003
Dysplasia	**Moderate vs Severe**	2.593	1.391	*4.834**	
Dysplasia	**None vs Severe**	1.333	0.774	2.296	
LI	**No vs Yes**	0.545	0.290	1.028	0.061

Significant at the 5% level

Overall, review of the final multivariate model (Table 5.14) shows that clinical lesion appearance was significantly related to Disease Free status (p=0.03) with a decreased odds of disease free status for erythroleukoplakic lesions at the time of first treatment compared with leukoplakia (OR 0.53, 95% CI 0.32 to 0.85). The extent of dysplasia determined by histopathology examination was also significantly related to Disease Free status (p=0.003) with the odds of Disease Free status being increased for mild dysplasia (OR 3.01, CI 1.66 to 5.46) and moderate dysplasia (OR 2.59, CI 1.39 to 4.83) versus severe dysplasia. To a lesser extent, Disease Free status was also less likely with increasing patient age and with lichenoid inflammation identified on initial, incision biopsy specimens.

The analyses were then repeated this time using the 'most significant' dysplasia diagnoses obtained from either incision or excision biopsy samples; univariate analyses are summarised in Tables 5.15a & 5.15b. Multivariate analysis was then performed, although PVL was again excluded as it was not significant in the univariate analysis (p=0.2887). Site was not included due to the large number of categories and its high correlation to other variables. All other variables were included as they reached the 0.2 level of significance univariately. Sex was removed in the first step (p=0.32), and age removed in the second step (p=0.15). All other factors were retained at the 10% level, and the results presented in Table 5.16.

TABLE 5.15: ANALYSIS OF CLINICO-PATHOLOGICAL FACTORS INFLUENCING DISEASE FREE STATUS SHOWING (A) RELATIONSHIP BETWEEN FACTORS AND (B) UNIVARIATE ANALYSIS *(BASED UPON 'MOST SIGNIFICANT' DYSPLASIA DIAGNOSIS)*

A

	Site	Age	Sex	Lesion	Most Significant Dysplasia	LI	PVL
Site	-	<0.0001	<0.0001	<0.0001	<0.0001	0.0007	<0.0001
Age		-	0.0654	0.1802	0.0021	0.0064	0.1154
Sex			-	0.0219	0.0679	0.007	0.0903
Lesion				-	<0.0001	0.2756	0.0002
Most Significant Dysplasia					-	0.0005	0.0002
LI						-	0.0011
PVL							-

p-values from chi-square tests for categorical variables or logistic regression for continuous variables

B

Factor	**Logistic p-value**
Site	0.0009
Age	0.0255
Sex	0.1124
Lesion	0.0001
Most Significant Dysplasia (None, Mild, Moderate vs Severe)	<0.0001
LI	0.0428
PVL	0.2887

TABLE 5.16: FINAL MULTIVARIATE MODEL OF CLINICO-PATHOLOGICAL INFLUENCE ON DISEASE FREE STATUS SHOWING ODDS RATIO ESTIMATES AND P-VALUES *(BASED UPON 'MOST SIGNIFICANT' DYSPLASIA DIAGNOSIS)*

Effect		**Point Estimate**	**95% Wald Confidence Limits**		**P-value**
Lesion	**EK vs LK**	0.659	0.269	1.619	0.022
Lesion	**ELK vs LK**	0.510	0.314	*0.828**	
Dysplasia	**Mild vs Severe**	2.247	1.270	*3.976**	<0.0001
Dysplasia	**Moderate vs Severe**	1.693	0.954	3.006	
Dysplasia	**None vs Severe**	0.628	0.369	1.068	
LI	**No vs Yes**	0.489	0.258	0.926	0.028

****Significant at the 5% level***

Table 5.16 shows that this final multivariate model confirms that the categories of clinical lesion appearance (p=0.022), dysplasia (p<0.0001) and lichenoid inflammation (p=0.028) were all significant predictors of Disease Free status. Thus, erythroleukoplakic lesions at the time of first treatment had significantly lower odds of achieving Disease Free status compared with leukoplakias (OR 0.51, 95% CI 0.31 to 0.83), whilst the odds of Disease Free status were significantly increased for lesions exhibiting mild versus severe dysplasia (OR 2.247, 95% CI 1.27 to 3.98). The likelihood of achieving Disease Free status was reduced for lesions exhibiting features of lichenoid inflammation on histopathological examination (OR 0.49, 95% CI 0.26 to 0.93).

5.4.7. Further / Disease Free Patients. 34 patients who developed further clinically recognisable oral potentially malignant lesions ultimately progressed to Disease Free status following subsequent laser intervention. Lesion clinical appearance is summarized in Table 5.17, and histopathology diagnoses listed in Table 5.18, although there are few clinical or histopathological differences in these features to distinguish or characterise this group from the other reported clinical outcome categories. In terms of anatomical site, the floor of mouth and ventrolateral tongue were most commonly affected in 16 cases (47%), with buccal mucosa next frequently involved in 9 (26%). All original patient data for this group can be accessed in Appendix V.

Table 5.19 collates all clinico-pathological, treatment and clinical outcome data for these 34 patients; 77 treatment episodes were identified in total for this cohort, carried out between August 1997 and December 2014. In Table 5.20, it can been seen that the mean number of treatments required to establish Disease Free status was 2.26 (with a range of 2 to 4) and a mean time period to become disease free of 32.88 months (but with a wide range of 4 to 130.9 months noted).

TABLE 5.17: CLINICAL APPEARANCE OF PMD LESIONS IN FURTHER / DISEASE FREE PATIENTS

Clinical Appearance	No. of Patients	%
Leukoplakia	25	74
Erythroleukoplakia	8	23
Erythroplakia	1	3
Total	34	100

TABLE 5.18: HISTOPATHOLOGY DIAGNOSES OF PMD LESIONS IN FURTHER / DISEASE FREE PATIENTS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	0	0.0
Hyperkeratosis + Lichenoid Inflammation (LI)	3	8.8
Chronic Hyperplastic Candidosis (CHC)	2	5.9
Proliferative Verrucous Leukoplakia (PVL)	1	2.9
Mild Dysplasia	6	17.6
Mild Dysplasia + LI	2	5.9
Mild Dysplasia + PVL	2	5.9
Moderate Dysplasia	1	2.9
Moderate Dysplasia + LI	4	11.8
Moderate Dysplasia + PVL	0	0.0
Severe Dysplasia	8	23.6
Severe Dysplasia + LI	1	2.9
Severe Dysplasia + PVL	0	0.0
Carcinoma-in-Situ	4	11.8
Total	34	100.0

TABLE 5.19: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR THE 34 FURTHER / DISEASE FREE PATIENTS

(No of Treatment Episodes = 77)

	StudyNo	No Of Trts	TRT NO	DATE	SEX	AGE	LESION	SITE	IN. BIOPSY	LASER EX.	STATUS	TRT	Outcome
1	1997/6	2	6	AUG1997	M	47	LK	FOM	CiS	CiS	Further	M	
2	1997/6	2	6	MAY2000	M	49	LK	FOM	Sev Dysp	Sev Dysp	DF	M	DF
3	1998/12	2	12	NOV1998	M	60	ELK	Buccal	Sev Dysp	Sev Dysp+LI	Further	M	
4	1998/12	2	12	JUN2005	M	66	LK	Buccal	Mild Dysp	HK+LI	DF	M	DF
5	1999/9	3	9	MAY1999	M	53	LK	FOM	Mod Dysp	CiS	Further	M	
6	1999/9	3	9	JUN2000	M	54	LK	FOM	Mod Dysp+LI	Sev Dysp	Further	M	
7	1999/9	3	9	SEP2001	M	56	LK	Lat Tongue	Mod Dysp+LI	Sev Dysp	DF	M	DF
8	2001/12	3	12	JUN2001	M	60	LK	FOM	Mod Dysp+LI	Sev Dysp	Further	M	
9	2001/12	3	12	JUL2003	M	62	LK	Vent Tongue	Mod Dysp	Mod Dysp	Further	M	
10	2001/12	3	12	DEC2004	M	64	LK	Lat Tongue	Mod Dysp	Mod Dysp	DF	M	DF
11	2001/5	2	5	FEB2001	F	58	LK	Buccal	Mod Dysp	Mod Dysp	Further	M	
12	2001/5	2	5	JUL2002	F	59	LK	Alveolus	Mod Dysp+LI	ABLATE	DF	M	DF
13	2002/16	2	16	DEC2002	M	45	LK	Gingiva	Mild Dysp	ABLATE	Further	M	
14	2002/16	2	16	SEP2013	M	58	LK	Labial	Mild Dysp	ABLATE	DF	M	DF
15	2002/9	2	9	OCT2002	F	64	ELK	FOM	CiS	CiS	Further	M	
16	2002/9	2	9	JUL2004	F	66	LK	Fauces	Sev Dysp	Sev Dysp	DF	M	DF
17	2004/18	2	18	JUL2004	F	55	LK	Palate	Sev Dysp	ABLATE	Further	M	
18	2004/18	2	18	FEB2005	F	56	LK	Fauces	Sev Dysp	CiS	DF	M	DF
19	2004/23	3	23	OCT2004	M	49	LK	Lat Tongue	CiS	CiS	Further	M	
20	2004/23	3	23	FEB2005	M	50	LK	Lat Tongue	CiS	CiS	Further	M	
21	2004/23	3	23	AUG2012	M	57	ELK	Lat Tongue	Mild Dysp	Mild Dysp	DF	M	DF
22	2006/6	2	6	MAR2006	M	83	LK	Lat Tongue	Sev Dysp	Sev Dysp	Further	M	
23	2006/6	2	6	JUN2007	M	84	LK	Vent Tongue	Mild Dysp+LI	Mod Dysp	DF	M	DF
24	2006/7	2	7	JUN2006	F	67	LK	Lat Tongue	Mild Dysp	Mod Dysp	Further	M	
25	2006/7	2	7	SEP2007	F	68	LK	Lat Tongue	Mild Dysp	Mild Dysp	DF	M	DF
26	2007/26	3	26	NOV2007	F	61	LK	Buccal	Sev Dysp	Sev Dysp	Further	M	
27	2007/26	3	26	MAR2011	F	64	ELK	Alveolus	HK+LI	ABLATE	Further	M	
28	2007/26	3	26	MAR2012	F	65	EK	Alveolus	Mod Dysp	ABLATE	DF	M	DF

	StudyNo	No Of Trts	TRT NO	DATE	SEX	AGE	LESION	SITE	IN. BIOPSY	LASER EX.	STATUS	TRT	Outcome
29	2008/3	2	3	FEB2008	M	43	ELK	FOM	HK+LI	Mild Dysp	Further	M	
30	2008/3	2	3	JUN2014	M	50	LK	FOM	Mild Dysp	ABLATE	DF	M	DF
31	2009/14	2	14	MAR2009	M	48	LK	Vent Tongue	Sev Dysp	Sev Dysp	Further	M	
32	2009/14	2	14	APR2010	M	49	LK	FOM	Sev Dysp	Sev Dysp+LI	DF	M	DF
33	2009/23	2	23	JUL2009	F	44	ELK	Dors Tongue	CHC	CHC	Further	M	
34	2009/23	2	23	JUN2014	F	49	LK	Dors Tongue	CHC	CHC	DF	M	DF
35	2009/33	3	33	OCT2009	F	63	ELK	Lat Tongue	Sev Dysp	Sev Dysp	Further	M	
36	2009/33	3	33	OCT2011	F	65	ELK	Lat Tongue	Sev Dysp	ABLATE	Further	M	
37	2009/33	3	33	JUL2012	F	66	LK	Vent Tongue	Mild Dysp	ABLATE	DF	M	DF
38	2009/40	4	40	NOV2009	M	68	ELK	FOM	Sev Dysp	CiS	Further	M	
39	2009/40	4	40	JUL2011	M	70	LK	FOM	CiS	ABLATE	Further	M	
40	2009/40	4	40	MAY2013	M	72	LK	FOM	Sev Dysp	Sev Dysp	Further	M	
41	2009/40	4	40	SEP2014	M	74	LK	Vent Tongue	Sev Dysp	Sev Dysp	DF	M	DF
42	2010/10	2	10	MAR2010	M	58	LK	Buccal	PVL	HK+LI	Further	M	
43	2010/10	2	10	OCT2010	M	58	LK	Labial Comm	HK+LI	PVL	DF	M	DF
44	2011/17	2	17	MAR2011	F	72	LK	FOM	PVL	Mild Dysp+LI	Further	M	
45	2011/17	2	17	JUN2013	F	74	LK	Buccal	Mild Dysp+LI	HK+LI	DF	M	DF
46	2011/24	3	24	MAY2011	M	65	LK	Palate	Sev Dysp	Mod Dysp	Further	M	
47	2011/24	3	24	NOV2012	M	66	LK	Lat Tongue	Mod Dysp	Mild Dysp	Further	M	
48	2011/24	3	24	NOV2014	M	68	ELK	RM	Sev Dysp	Sev Dysp	DF	M	DF
49	2011/27	2	27	MAY2011	F	45	LK	Palate	Mild Dysp	Mild Dysp	Further	M	
50	2011/27	2	27	MAR2014	F	48	LK	Palate	Mild Dysp	ABLATE	DF	M	DF
51	2011/3	2	3	JAN2011	M	57	LK	Palate	Mod Dysp+LI	Mod Dysp	Further	M	
52	2011/3	2	3	MAY2012	M	59	LK	Palate	Mod Dysp	Mod Dysp	DF	M	DF
53	2011/34	2	34	JUN2011	M	47	LK	Labial Comm	CHC	CHC	Further	M	
54	2011/34	2	34	JUN2013	F	49	LK	Labial Comm	CHC	ABLATE	DF	M	DF
55	2011/50	2	50	SEP2011	M	74	LK	Lat Tongue	MildDyspPVL	Mild Dysp	Further	M	
56	2011/50	2	50	JUL2012	M	75	LK	Buccal	Mild Dysp	Mild Dysp	DF	M	DF
57	2011/51	3	51	SEP2011	M	46	ELK	Labial Comm	CHC	MildDyspPVL	Further	M	
58	2011/51	3	51	DEC2013	M	47	LK	Vent Tongue	Sev Dysp	ModDyspPVL	Further	M	

	StudyNo	No Of Trts	TRT NO	DATE	SEX	AGE	LESION	SITE	IN. BIOPSY	LASER EX.	STATUS	TRT	Outcome
59	2011/51	3	51	DEC2014	M	48	LK	Labial Comm	MildDyspPVL	ABLATE	DF	M	DF
60	2011/62	2	62	DEC2011	F	57	LK	Gingiva	HK+LI	ABLATE	Further	M	
61	2011/62	2	62	JUN2014	F	60	LK	Gingiva	HK+LI	ABLATE	DF	M	DF
62	2011/9	2	9	FEB2011	F	77	LK	Buccal	PVL	Mild Dysp	Further	M	
63	2011/9	2	9	JUN2013	F	79	LK	Buccal	Mild Dysp+LI	HK+LI	DF	M	DF
64	2012/24	2	24	JUN2012	F	51	LK	Buccal	PVL	PVL	Further	M	
65	2012/24	2	24	MAY2013	F	52	LK	Buccal	Mild Dysp	MildDyspPVL	DF	M	DF
66	2013/1	2	1	JAN2013	M	70	ELK	Buccal	HK+LI	Mild Dysp+LI	Further	M	
67	2013/1	2	1	MAY2013	M	71	ELK	Buccal	HK+LI	HK+LI	DF	M	DF
68	2013/30	2	30	MAY2013	F	60	LK	Alveolus	HK+LI	ABLATE	Further	M	
69	2013/30	2	30	JUN2014	F	61	LK	FOM	Mild Dysp	Mild Dysp	DF	M	DF
70	2013/34	2	34	MAY2013	M	47	LK	FOM	Mild Dysp	Mild Dysp	Further	M	
71	2013/34	2	34	MAY2014	M	48	LK	FOM	Mild Dysp	Mild Dysp	DF	M	DF
72	2013/42	2	42	JUN2013	F	52	LK	Lat Tongue	Mod Dysp	Sev Dysp	Further	M	
73	2013/42	2	42	MAY2014	F	53	LK	Lat Tongue	Mod Dysp+LI	Sev Dysp	DF	M	DF
74	2013/5	2	5	JAN2013	M	54	EK	Fauces	Mod Dysp	Sev Dysp	Further	M	
75	2013/5	2	5	FEB2014	M	55	LK	Fauces	Mod Dysp	Sev Dysp	DF	M	DF
76	2013/54	2	54	AUG2013	F	63	LK	FOM	Mild Dysp	Mild Dysp	Further	M	
77	2013/54	2	54	JUN2014	F	64	LK	Palate	Mild Dysp	Mild Dysp	DF	M	DF

TABLE 5.20: NUMBER OF TREATMENTS REQUIRED AND TIME (IN MONTHS) TO ESTABLISH DISEASE FREE STATUS

(No of Patients = 34)

	Mean	Median	SD	SE	Max	Min	No
No of Treatments	2.26	2.00	0.51	0.09	4.00	2.00	34
No of Months	32.88	25.90	28.55	4.90	130.90	4.00	34

5.4.8. Further / Persistent Disease Patients. During the study period, 53 patients exhibited Further/Persistent PMD disease despite interventional treatment and their clinical features and histopathological diagnoses, which are relatively consistent with previous outcome categories, are presented in Tables 5.21 and 5.22. Floor of mouth and ventrolateral sites were again most commonly affected by disease (17 or 32%), but buccal (14 or 26%) and especially gingiva / alveolus sites (11 or 21%) were also involved more frequently (although non-significantly) in this persistent disease group. Full details on these patients can be found in Appendix V.

Table 5.23 collates clinico-pathological, treatment and clinical outcome data for these 53 patients and shows that 38 patients (72%) underwent only 1 treatment intervention, whilst the remaining 15 (28%) experienced 2 to 4 treatment episodes.

Table 5.24 directly compares clinico-pathological features, treatment and clinical outcome data from the 34 Further/Disease Free patient group with this 53 patient Further/Persistent Disease group to assess the influence of age, sex, clinical appearance, anatomical site, histopathological diagnosis, treatment and follow-up on outcome status. The only statistically significant difference seen was in the number of treatment interventions, which were exclusively administered as multiple interventions in the Further / Disease Free study group; $p<0.0001$.

Although not of statistical significance by chi-square testing ($p=0.47$), review of the percentage of patients exhibiting characteristics of proliferative verrucous leukoplakia (PVL) on histopathology examination revealed a much higher occurrence in the Further/Persistent Disease group (37.6%) compared with much lower levels seen in all other clinical outcome categories: a figure of 12.5% overall for the 590 PMD lesions, 12.4% in the Disease Free cases and 8.8% in Further/Disease Free patients. These data are listed in Tables 5.3, 5.12 and 5.18.

TABLE 5.21: CLINICAL APPEARANCE OF PMD LESIONS IN FURTHER / PERSISTENT DISEASE PATIENTS

Clinical Appearance	No. of Patients	%
Leukoplakia	45	85
Erythroleukoplakia	6	11
Erythroplakia	2	4
Total	53	100

TABLE 5.22: HISTOPATHOLOGY DIAGNOSES OF PMD LESIONS IN FURTHER / PERSISTENT DISEASE PATIENTS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	1	1.9
Hyperkeratosis + Lichenoid Inflammation (LI)	2	3.8
Chronic Hyperplastic Candidosis (CHC)	0	0.0
Proliferative Verrucous Leukoplakia (PVL)	7	13.2
Mild Dysplasia	7	13.2
Mild Dysplasia + LI	3	5.7
Mild Dysplasia + PVL	9	16.9
Moderate Dysplasia	6	11.3
Moderate Dysplasia + LI	3	5.7
Moderate Dysplasia + PVL	4	7.5
Severe Dysplasia	8	15.1
Severe Dysplasia + LI	1	1.9
Severe Dysplasia + PVL	0	0.0
Carcinoma-in-Situ	2	3.8
Total	53	100.0

TABLE 5.23: CLINICO-PATHOLOGICAL, TREATMENT AND CLINICAL OUTCOME DETAILS FOR THE 53 FURTHER / PERSISTENT DISEASE PATIENTS

	Study No	SEX	AGE	LESION	SITE	HISTOPATHOLOGY (Most Significant)	TREATMENT	SITE OF PERSISTENT DISEASE	No of Trts
1	2000/12	F	54	LK	Alveolus	Mod Dysp+LI	Ablation	Same	1
2	2000/33	M	59	LK	Ventral Tongue	Mod Dysp	Excision	New	2
3	2001/13	M	55	ELK	Fauces	CiS	Excision	Same	1
4	2001/16	F	65	LK	Gingiva	Mild Dysp	Ablate	Same	1
5	2002/8	M	41	LK	FOM	CiS	Excision	New	4
6	2002/10	M	27	LK	FOM	Mod Dysp+LI	Excision	Same	1
7	2003/6	F	67	EK	Buccal	Sev Dysp	Excision	New	2
8	2005/2	M	69	LK	FOM	Mod Dysp	Excision	Same	1
9	2005/4	M	55	LK	Lateral Tongue	CiS	Excision	Same	1
10	2006/11	M	56	LK	FOM	Sev Dysp	Excision	Same	1
11	2006/17	F	93	EK	Buccal	Sev Dysp	Excision	Same	1
12	2007/7	F	58	LK	FOM	Mild Dysp	Ablate	New	3
13	2008/11	M	56	LK	Lateral Tongue	Sev Dysp	Excision	Same	2
14	2008/28	F	67	LK	Palate	Mild Dysp	Excision	New	3
15	2009/10	M	52	LK	Labial Comm	Mild Dysp	Excision	Same	1
16	2010/6	M	69	LK	FOM	Mild Dysp+LI	Excision	New	1
17	2010/8	M	67	ELK	Lateral Tongue	Mild Dysp+LI	Excision	Same	1
18	2010/19	M	72	LK	Alveolus	PVL	Excision	New	1
19	2010/28	F	56	ELK	Labial Comm	Mod Dysp	Excision	New	1
20	2010/30	M	70	LK	Buccal	ModDyspPVL	Excision	New	2
21	2010/34	F	59	LK	Palate	HK	Ablate	Same	1
22	2010/39	M	79	LK	Alveolus	MildDyspPVL	Excision	Same	3
23	2011/1	M	63	LK	Labial	Sev Dysp+LI	Ablate	Same	1
24	2011/11	F	61	LK	Fauces	ModDyspPVL	Excision	New	1
25	2011/12	F	70	LK	Buccal	ModDyspPVL	Excision	New	1
26	2011/22	M	42	LK	Labial	Mild Dysp	Ablate	Same	2
27	2011/38	M	38	LK	Buccal	MildDyspPVL	Excision	Same	1
28	2011/48	F	56	ELK	Lateral Tongue	Mod Dysp	Excision	New	3
29	2011/49	M	74	LK	Labial	MildDyspPVL	Excision	New	1

	Study No	SEX	AGE	LESION	SITE	HISTOPATHOLOGY (Most Significant)	TREATMENT	SITE OF PERSISTENT DISEASE	No of Trts
30	2011/58	F	58	LK	Gingiva	MildDyspPVL	Ablate	Same	1
31	2011/60	M	49	ELK	Labial Comm	MildDyspPVL	Excision	New	3
32	2011/61	M	68	LK	Alveolus	Mild Dysp	Ablate	New	1
33	2012/2	F	62	LK	FOM	ModDyspPVL	Excision	Same	3
34	2012/3	M	51	LK	Buccal	HK+LI	Excision	Same	1
35	2012/5	M	80	LK	Buccal	Mod Dysp	Ablate	New	1
36	2012/15	F	24	LK	FOM	Mild Dysp+LI	Excision	Same	1
37	2012/18	F	57	LK	Dorsum Tongue	MildDyspPVL	Excision	Same	1
38	2012/20	F	56	ELK	Lateral Tongue	Sev Dysp	Excision	Same	1
39	2012/39	M	64	LK	Gingiva	PVL	Excision	New	1
40	2012/40	M	58	LK	Ventral Tongue	Mod Dysp	Excision	Same	1
41	2012/41	F	71	LK	Buccal	MildDyspPVL	Excision	New	1
42	2012/48	M	59	LK	Ventral Tongue	Sev Dysp	Excision	Same	1
43	2013/3	F	83	LK	Buccal	HK+LI	Excision	Same	1
44	2013/6	M	56	LK	Labial	PVL	Ablate	Same	1
45	2013/15	M	75	LK	Gingiva	PVL	Ablate	New	2
46	2013/19	F	63	LK	Alveolus	HK+LI	Ablate	Same	1
47	2013/47	M	68	LK	Alveolus	PVL	Excision	Same	1
48	2013/69	M	82	LK	Palate	PVL	Ablate	Same	2
49	2013/71	M	59	LK	Lateral Tongue	Mod Dysp+LI	Excision	Same	1
50	2013/72	F	73	LK	Labial	Sev Dysp	Excision	Same	1
51	2014/14	F	53	LK	FOM	MildDyspPVL	Excision	New	2
52	2014/19	F	65	LK	Gingiva	PVL	Ablate	Same	1
53	2014/25	M	63	LK	Buccal	Sev Dysp	Excision	Same	1

TABLE 5.24: COMPARISON OF CLINICO-PATHOLOGICAL FEATURES BETWEEN FURTHER / DISEASE FREE AND FURTHER / PERSISTENT DISEASE PATIENT GROUPS

		Further / DF *(n = 34)*		**Further / Persistent** *(n = 53)*	
		Value	*(%)*	**Value**	*(%)*
Age (Years)	Mean	57.7		61.0	
	Median	57.5		61.0	
	SD	10.3		12.6	
	SE	1.8		1.7	
	Max	83.0		93.0	
	Min	43.0		24.0	
Sex	Female	16	*(47)*	22	*(42)*
	Male	18	*(53)*	31	*(58)*
Follow-Up (Months)	Mean	80.7		61.0	
	Median	60.9		42.6	
	SD	57.8		48.3	
	SE	9.9		6.6	
	Max	212.3		180.6	
	Min	17.2		4.0	
Clinical Lesion	Leukoplakia	25	*(74)*	45	*(85)*
	Erythroleukoplakia	8	*(23)*	6	*(11)*
	Erythroplakia	1	*(3)*	2	*(4)*
Site	Floor of Mouth	9	*(26)*	8	*(15)*
	Ventro-Lateral Tongue	7	*(21)*	9	*(17)*
	Dorsum Tongue	1	*(3)*	1	*(2)*
	Buccal	9	*(26)*	14	*(26)*
	Fauces / Retromolar	1	*(3)*	2	*(4)*
	Gingiva / Alveolus	3	*(9)*	11	*(21)*
	Labial	0	*(0)*	5	*(9)*
	Palate	4	*(12)*	3	*(6)*

		Further / DF ***(n = 34)***		**Further / Persistent** ***(n = 53)***	
		Value	***(%)***	**Value**	***(%)***
Dysplasia	None	9	*(26)*	14	*(26)*
	Mild	9	*(26)*	16	*(30)*
	Moderate	3	*(9)*	13	*(25)*
	Severe	13	*(39)*	10	*(19)*
PVL	No	29	*(85)*	35	*(66)*
	Yes	5	*(15)*	18	*(34)*
Lichenoid Inflammation	No	28	*(82)*	43	*(81)*
	Yes	6	*(18)*	10	*(19)*
Treatment Intervention	Multiple	34	*(100)*	15	*(28)*
	Single	0	*(0)*	38	*(72)*

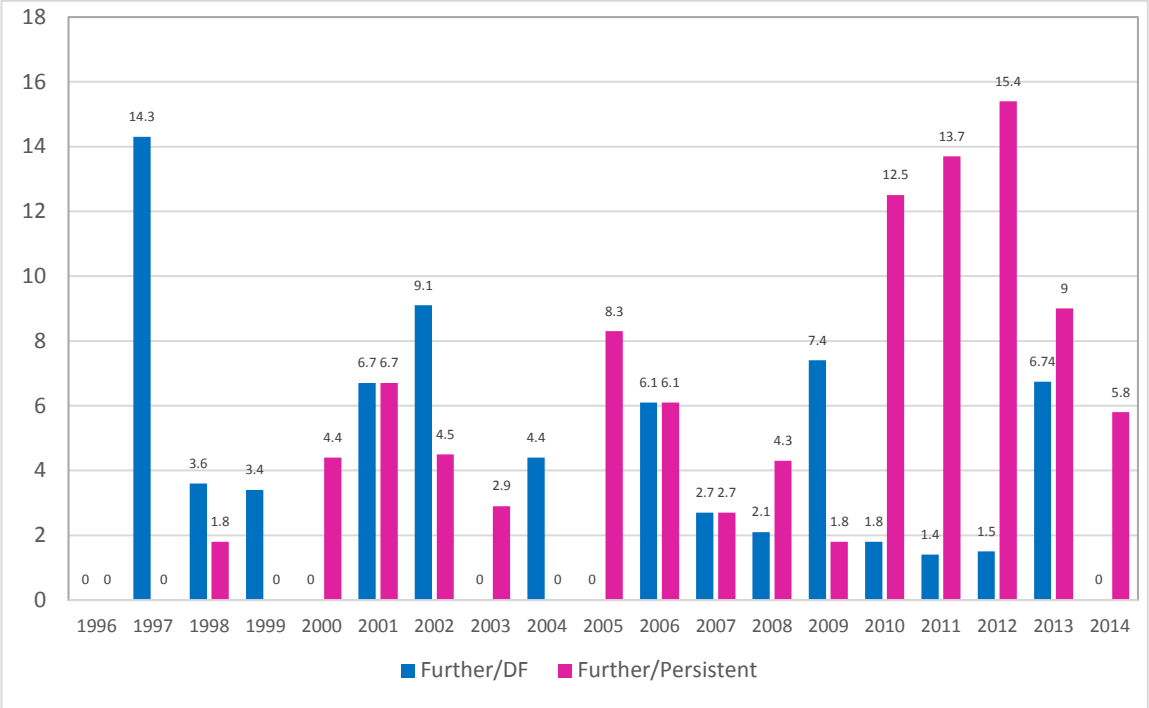
	Test	**p-value**
Age	t-test	p=0.21
Sex	Chi-square	p=0.61
Follow-Up	Wilcoxon rank sum	p=0.08
Clinical Lesion	Fisher's exact	p=0.27
Site	Fisher's exact	p=0.55
Dysplasia	Chi-square	p=0.12
PVL	Chi-square	p=0.47
Lichenoid Inflammation	Chi-square	p=0.89
Treatment Intervention	Chi-square	p<0.0001

The numbers of patients who developed Further/Disease Free and Further/Persistent Disease status are listed against their year of first clinical presentation in Table 5.25, and the corresponding percentage figures illustrated in Figure 5.5. There appears to be a trend for an increasing percentage of patients to exhibit Further/Persistent Disease from around 2010 onwards, although the actual number of patients affected (3 to 10 per year) remains small.

TABLE 5.25: NUMBERS (AND PERCENTAGES) OF FURTHER / DISEASE FREE AND FURTHER / PERSISTENT DISEASE PATIENTS PRESENTING EACH STUDY YEAR

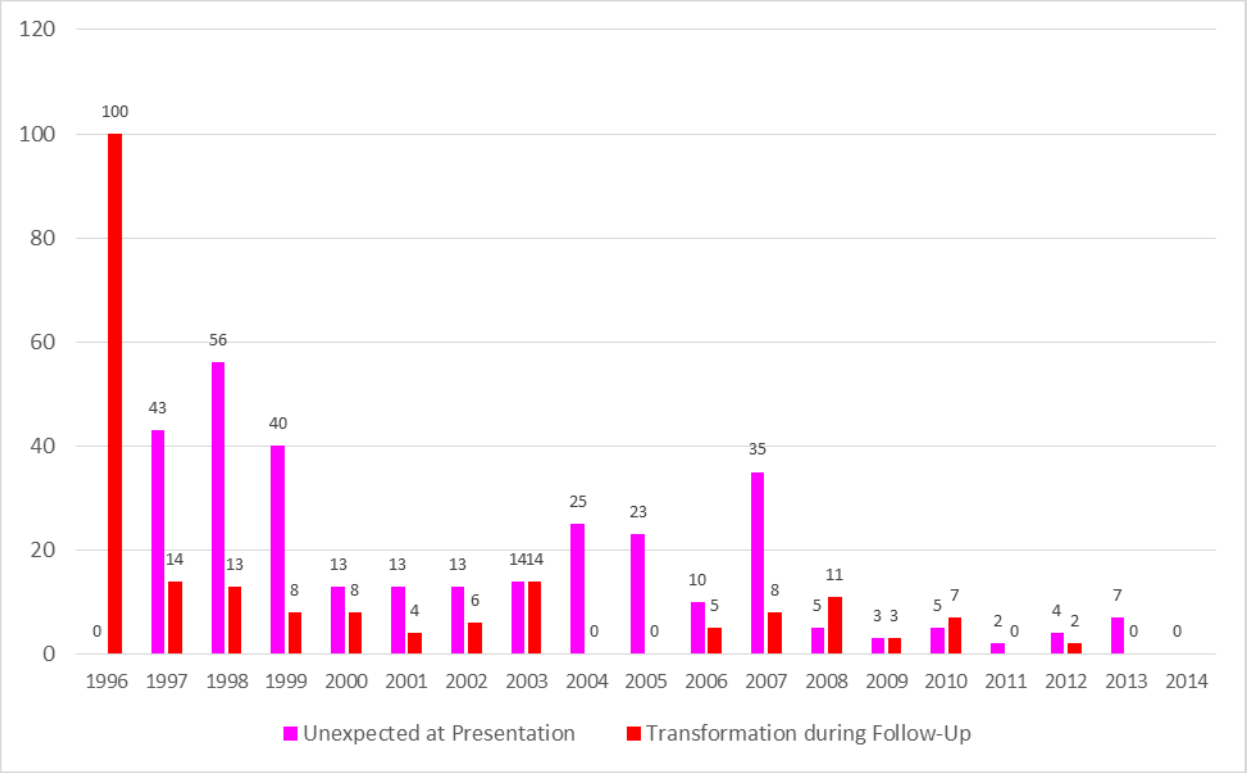
Year	Total No. of Patients	No. of Further /Disease Free	%	No. of Further/Persistent Disease	%
1996	2	0	*0*	0	*0*
1997	7	1	*14.3*	0	*0*
1998	28	1	*3.6*	0	*0*
1999	29	1	*3.4*	0	*0*
2000	45	0	*0*	2	*4.4*
2001	30	2	*6.7*	2	*6.7*
2002	22	2	*9.1*	1	*4.5*
2003	34	0	*0*	1	*2.9*
2004	45	2	*4.4*	0	*0*
2005	24	0	*0*	2	*8.3*
2006	33	2	*6.1*	2	*6.1*
2007	37	1	*2.7*	1	*2.7*
2008	47	1	*2.1*	2	*4.3*
2009	54	4	*7.4*	1	*1.8*
2010	56	1	*1.8*	7	*12.5*
2011	73	9	*1.4*	10	*13.7*
2012	65	1	*1.5*	10	*15.4*
2013	89	6	*6.74*	8	*9.0*
2014	52	0	*0*	3	*5.8*

Figure 5.5: Percentage of Further/Disease Free (DF) and Further/Persistent Disease Patients plotted against study year of first presentation (1996 to 2014).



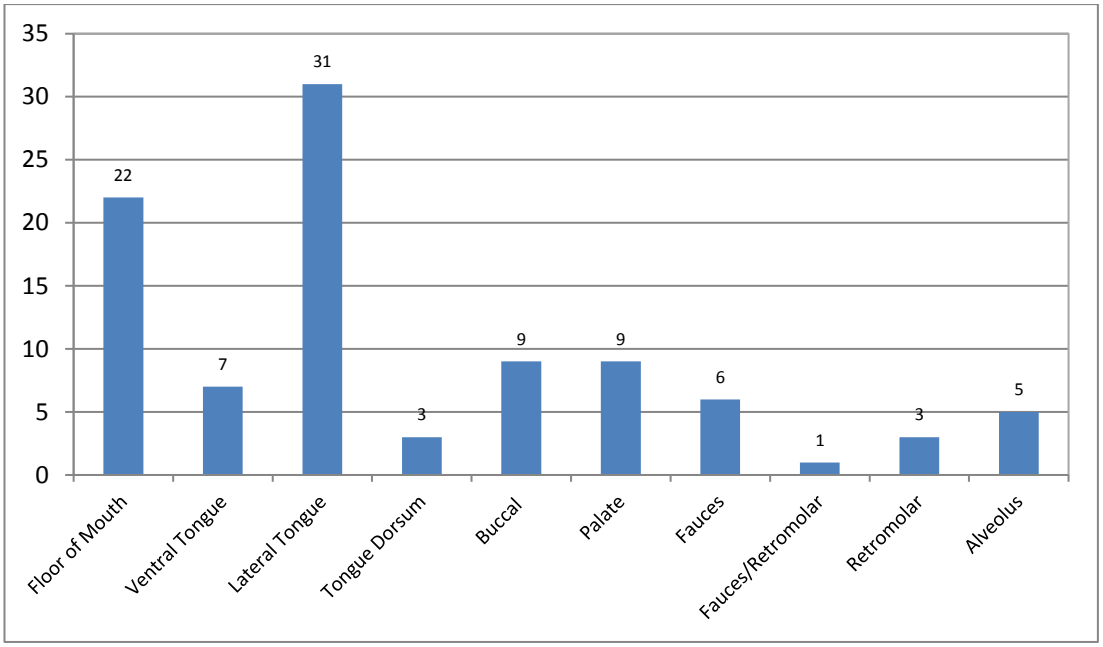
5.4.9. Malignant Transformation Patients. 99 out of 590 treated PMD patients (16.8%) developed an oral squamous cell carcinoma during the study period. Importantly, 71 (12%) were identified upon histopathological assessment of initial laser excision specimens, with only 28 patients (4.8%) progressing to malignancy during subsequent follow-up. Original patient data for this group can be reviewed in Appendix V. Figure 5.6 illustrates the overall pattern of malignant disease presentation during the study period.

Figure 5.6: Percentage of PMD Cases undergoing Malignant Transformation (both unexpected at initial presentation and during follow-up) plotted against Year of Initial PMD Precursor Lesion Presentation.



The anatomical site distribution of the 99 precursor lesions is illustrated in Figure 5.7; the floor of mouth and ventro-lateral tongue sites accounted for the majority of cases (60). Overall, 80 carcinomas developed at the same site as their precursor lesions, whilst 19 tumours presented at new intra-oral sites.

Figure 5.7: Anatomical Site Distribution of Presenting PMD Lesions in Patients Undergoing Malignant Transformation (total number of lesions = 99).



The clinical appearance of the 99 presenting PMD lesions are recorded in Table 5.26, showing a much higher percentage of erythroleukoplakia lesions (48%) and a corresponding reduction in leukoplakia (48%) compared to other specific outcome categories (documented in Tables 5.11, 5.17 and 5.21). The histopathological profiles of the lesions are listed in Table 5.27 and are presented graphically in Figure 5.8 to demonstrate the much higher percentage of severe dysplasia and carcinoma-in-situ diagnoses seen in the malignant transformation group (64.6% in total) compared with Disease Free (25.7%), Further / Disease Free (38.3%), and Further / Persistent Disease (20.8%) patient groups; Tables 5.12, 5.18 and 5.22, respectively.

TABLE 5.26: CLINICAL APPEARANCE OF PMD LESIONS IN MALIGNANT TRANSFORMATION PATIENTS

Clinical Appearance	No. of Patients	%
Leukoplakia	48	48
Erythroleukoplakia	47	48
Erythroplakia	4	4
Total	99	100

TABLE 5.27: HISTOPATHOLOGY DIAGNOSES OF PMD LESIONS IN MALIGNANT TRANSFORMATION PATIENTS

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	2	2.0
Hyperkeratosis + Lichenoid Inflammation (LI)	3	3.0
Chronic Hyperplastic Candidosis (CHC)	1	1.0
Proliferative Verrucous Leukoplakia (PVL)	1	1.0
Mild Dysplasia	11	11.1
Mild Dysplasia + LI	1	1.0
Mild Dysplasia + PVL	0	0.0
Moderate Dysplasia	16	16.3
Moderate Dysplasia + LI	0	0.0
Moderate Dysplasia + PVL	0	0.0
Severe Dysplasia	32	32.3
Severe Dysplasia + LI	0	0.0
Severe Dysplasia + PVL	0	0.0
Carcinoma-in-Situ	32	32.3
Total	99	100.0

Figure 5.8: Histopathology of Presenting PMD Lesions in Patients Undergoing Malignant Transformation (total number of lesions = 99; *HK* Hyperkeratosis, *LI* Lichenoid Inflammation, *CHC* Chronic Hyperplastic Candidosis, *Dysp* Dysplasia, *CiS* Carcinoma-in-Situ).

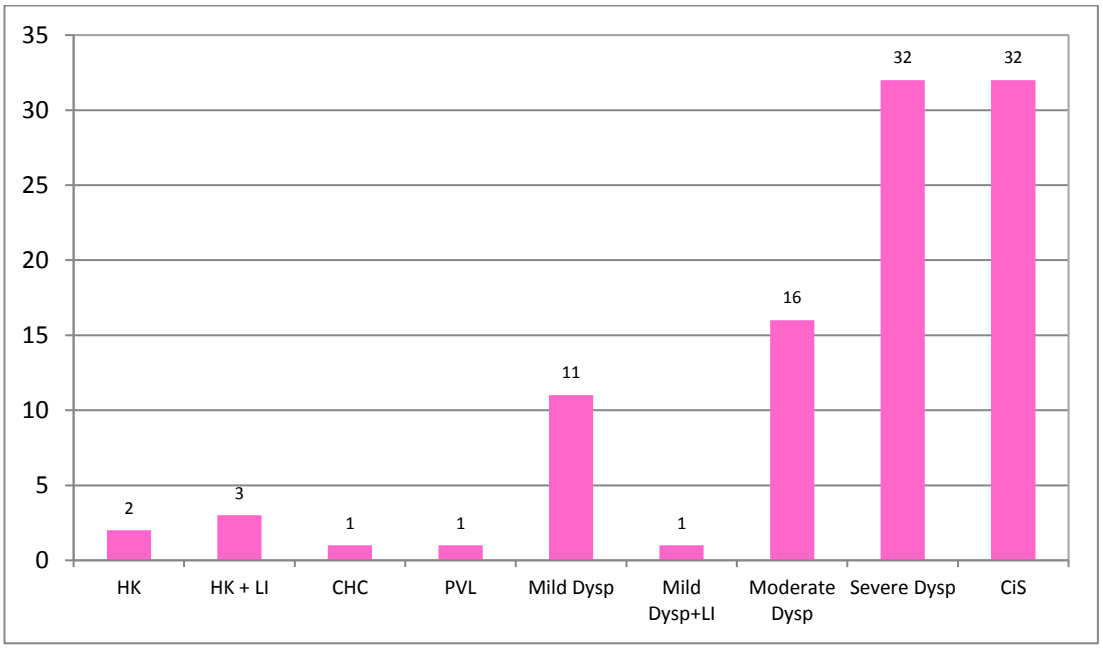


Table 5.28 summarizes overall clinico-pathological data for the 71 presenting PMD lesions cases in which 'unexpected' SCC was diagnosed following histopathological inspection of laser excision biopsy specimens.

TABLE 5.28: CLINICO-PATHOLOGICAL FEATURES OF PRECURSOR PMD LESIONS WHERE LASER EXCISION REVEALED UNEXPECTED SCC (*Number = 71*)

Patient No.	PMD Lesion	Lesion Site	Incision Biopsy Histopathology
1997/4	ELK	Buccal	Sev Dysp
1997/5	LK	Lateral Tongue	Mod Dysp
1997/7	LK	Buccal	HK
1998/1	ELK	Lateral Tongue	CiS
1998/3	ELK	Lateral Tongue	Sev Dysp
1998/4	LK	FOM	CiS
1998/6	ELK	Fauces	Sev Dysp
1998/8	ELK	Lateral Tongue	Sev Dysp
1998/9	EK	RM	CiS
1998/13	LK	Lateral Tongue	CiS
1998/15	ELK	Lateral Tongue	Sev Dysp
1998/16	ELK	Buccal	CHC
1999/2	LK	Lateral Tongue	Sev Dysp
1999/3	LK	Lateral Tongue	Sev Dysp
1999/4	LK	FOM	Mod Dysp
1999/5	ELK	Lateral Tongue	Sev Dysp
1999/6	ELK	FOM	Mod Dysp
1999/8	ELK	FOM	CiS
1999/15	ELK	Palate	CiS
1999/16	ELK	FOM	CiS
1999/19	ELK	Lateral Tongue	Sev Dysp
1999/21	LK	Buccal	Sev Dysp
2000/17	LK	Ventral Tongue	CiS
2000/19	LK	Palate	CiS
2000/20	LK	Lateral Tongue	CiS
2000/29	LK	FOM	CiS
2000/30	LK	Palate	CiS
2001/8	EK	Fauces / RM	CiS
2001/15	ELK	Fauces	CiS
2001/24	LK	Buccal	CiS
2002/1	LK	Ventral Tongue	HK
2002/4	ELK	FOM	Sev Dysp
2003/11	LK	Alveolus	Sev Dysp
2003/19	LK	Lateral Tongue	Sev Dysp
2003/20	LK	Ventral Tongue	CiS
2003/25	LK	Lateral Tongue	CiS
2004/4	LK	Lateral Tongue	HK + LI
2004/9	LK	FOM	CiS
2004/10	ELK	Lateral Tongue	CiS
2004/15	LK	FOM	Sev Dysp
2004/16	ELK	Lateral Tongue	CiS
2004/25	LK	Lateral Tongue	CiS
2004/27	LK	Ventral Tongue	Mild Dysp
2004/29	LK	FOM	Sev Dysp

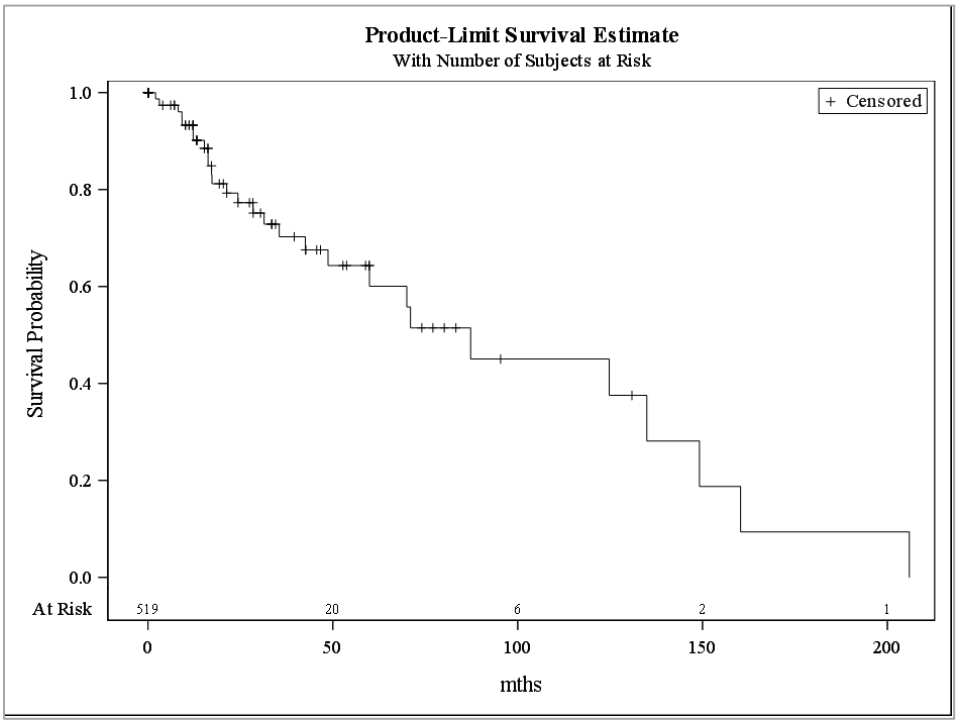
2005/11	ELK	FOM	Sev Dysp
2005/12	ELK	FOM	CiS
2005/13	ELK	Lateral Tongue	Sev Dysp
2006/9	LK	Dorsum Tongue	Mild Dysp
2006/18	ELK	RM	Sev Dysp
2007/1	LK	Lateral Tongue	CiS
2007/2	ELK	Lateral Tongue	Mod Dysp
2007/6	EK	Fauces	CiS
2007/9	LK	Lateral Tongue	Mod Dysp
2007/10	ELK	Buccal	Mod Dysp
2007/11	LK	Dorsum Tongue	PVL
2007/12	ELK	Ventral Tongue	Sev Dysp
2007/14	EK	Palate	Sev Dysp
2007/18	LK	Buccal	Mild Dysp
2008/26	LK	Lateral Tongue	Mild Dysp + LI
2008/38	LK	FOM	Sev Dysp
2009/11	LK	Ventral Tongue	Mod Dysp
2010/11	ELK	FOM	Sev Dysp
2010/33	LK	Lateral Tongue	Mild Dysp
2011/32	LK	FOM	Sev Dysp
2012/37	ELK	Alveolus	Mild Dysp
2012/52	LK	Fauces	Sev Dysp
2013/14	ELK	Lateral Tongue	CiS
2013/16	LK	FOM	Sev Dysp
2013/24	ELK	Lateral Tongue	Sev Dysp
2013/56	LK	Lateral Tongue	Mild Dysp
2013/66	ELK	Fauces	CiS

Clinico-pathological details of the 28 cases that progressed to malignancy during follow-up are listed in Table 5.29. Same site transformation occurred in 9 cases between 3 and 48 months (mean 28 months) post-laser, whilst new site transformation in 19 cases generally took longer, varying between 9 to 204 months (mean 61.3 months). Figure 5.9 illustrates the Kaplan-Meier survival curve of time to malignant transformation; patients whose carcinoma diagnosis was made at the time of first interventional treatment were excluded leaving 519 patients in the analysis. Patients who did not undergo malignant transformation by the study census date were censored in the Kaplan-Meier plot at the time of most recent follow-up. Overall, the median time to malignancy in the 28 transforming cases was 87.3 months (95% CI 59.9 to 149.2).

TABLE 5.29: CLINICO-PATHOLOGICAL FEATURES OF PRECURSOR PMD LESIONS AND CORRESPONDING TRANSFORMED SCC LESIONS (*Number = 28*)

Patient No	Precursor Lesion	Precursor Histopathology	Precursor Site	SCC Lesion	SCC Site	MT (months)	MT Site
1996/1	LK	Mod Dysp	Buccal	LK	Alveolus	204	New
1996/2	LK	HK + LI	Alveolus	LK	Palate	30	New
1997/3	LK	CiS	Fauces/RM	ELK	RM	48	Same
1998/5	EK	CiS	Fauces/RM	LK	L Tongue	8	New
1998/7	EK	CiS	Buccal	ELK	Alveolus	86	New
1999/17	LK	Mod Dysp	V Tongue	LK	L Tongue	15	New
1999/22	LK	Mod Dysp	L Tongue	LK	Buccal	12	New
2000/3	LK	Mod Dysp	Palate	ELK	Alveolus	124	New
2000/31	LK	CiS	L Tongue	ELK	FOM	133	New
2000/37	LK	CiS	Lab Com	ELK	D Tongue	147	New
2001/10	ELK	CiS	Fauces	ELK	Palate	158	New
2002/7	LK	Mod Dysp	Lab Com	LK	Labial	9	New
2003/1	LK	Sev Dysp	L Tongue	ELK	L Tongue	35	Same
2003/7	LK	CiS	L Tongue	LK	FOM	12	New
2003/9	LK	Mod Dysp	Alveolus	ELK	Buccal	69	New
2003/12	ELK	Sev Dysp	L Tongue	ELK	L Tongue	59	Same
2006/1	LK	Mild Dysp	L Tongue	ELK	Palate	18	New
2007/4	ELK	Sev Dysp	L Tongue	ELK	Palate	70	New
2007/5	LK	CiS	Fauces	ELK	FOM	17	New
2008/17	LK	Mild Dysp	Palate	ELK	Palate	3	Same
2008/20	LK	Sev Dysp	FOM	ELK	FOM	4	Same
2008/23	LK	Mild Dysp	Buccal	LK	Labial	28	New
2008/30	EK	CiS	FOM	LK	FOM	16	Same
2009/36	ELK	Sev Dysp	L Tongue	ELK	L Tongue	24	Same
2010/5	LK	Mild Dysp	V Tongue	ELK	V Tongue	42	Same
2010/9	ELK	Sev Dysp	L Tongue	ELK	Fauces	9	New
2010/22	ELK	Sev Dysp	FOM	ELK	Labial	16	New
2012/4	LK	Sev Dysp	FOM	LK	FOM	21	Same

Figure 5.9: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) for PMD Precursor Lesions.



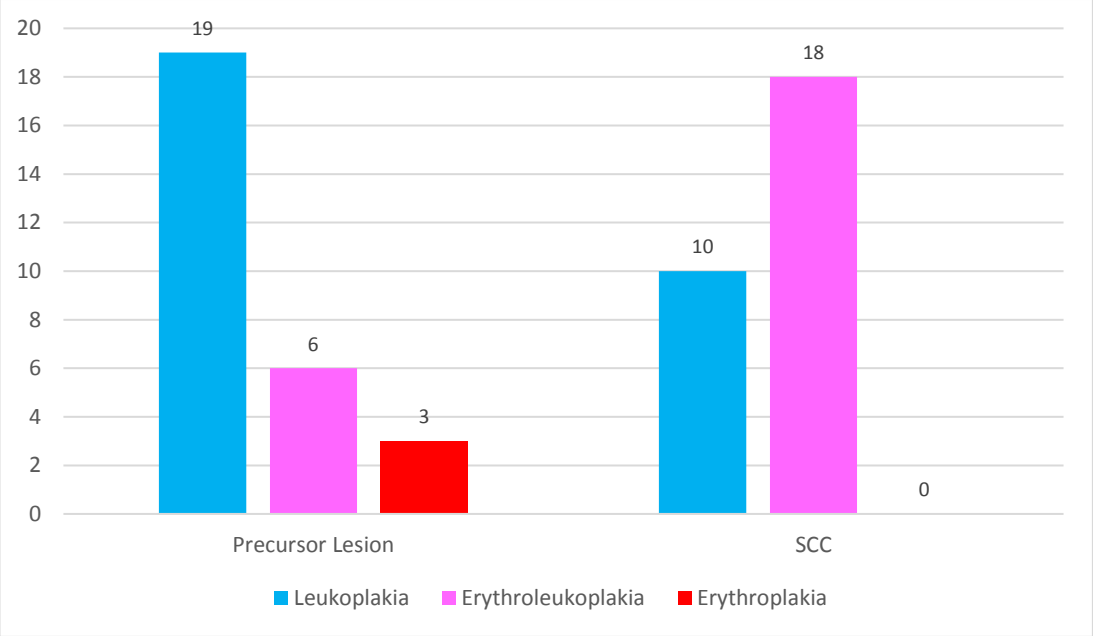
In terms of clinical appearance, Table 5.30 and Figure 5.10 directly compare precursor PMD lesions with their SCC transformed appearance, demonstrating that lesions presenting as erythroleukoplakia were significantly more likely to exhibit malignancy (p=0.0019; Fisher's exact test).

TABLE 5.30: CLINICAL APPEARANCE OF PRECURSOR PMD LESIONS AND TRANSFORMED SCC LESIONS

	Leukoplakia	Erythroleukoplakia	Erythroplakia	Totals
Precursor Lesion	19 (68%)	6 (21%)	3 (11%)	28 (100%)
SCC	10 (36%)	18 (64%)	0 (0%)	28 (100%)

Fisher's exact test p=0.0019

Figure 5.10: Change in Clinical Appearance between Precursor PMD Lesions and Transformed SCC Lesions (number of cases = 28).



Univariate Cox regression analyses of clinico-pathological variables which might influence the time to malignant transformation, including patient sex, age, anatomical site, clinical appearance, dysplasia grading (most significant from combined incision and excision biopsies), identification of PVL features and lichenoid inflammation on histopathology, were carried out but none showed a significant influence at the 5% level. This, however, is likely to have been influenced by the small sample size of this population (28). P-values for these data are summarised in Table 5.31, except for the categories of lesion site and PVL identification in which insufficient data was available in each category for estimation, and additionally graphically represented as Kaplan-Meier analyses in Figures 5.11 to 5.17.

TABLE 5.31: CLINICO-PATHOLOGICAL VARIABLES INFLUENCING MALIGNANT TRANSFORMATION (p-Values)

Clinico-Pathological Variable	p-Value
Sex	0.58
Age	0.46*
Site of Initial Presentation**	-
Clinical Appearance	0.55
Dysplasia Grading (WHO)	0.96
Dysplasia Grading (Binary)	0.86
Proliferative Verrucous Leukoplakia**	-
Presence of Lichenoid Inflammation	0.70

*Analysis of Maximum Likelihood Estimates						
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
Age	1	0.01176	0.01592	0.5463	0.4598	1.012

***Insufficient data available in category for analysis*

Figure 5.11: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against Sex of Patient: Females 124.8, 95%CI 31.4-160.3; Males 87.3 95%CI 48.7-149.2; p=0.58.

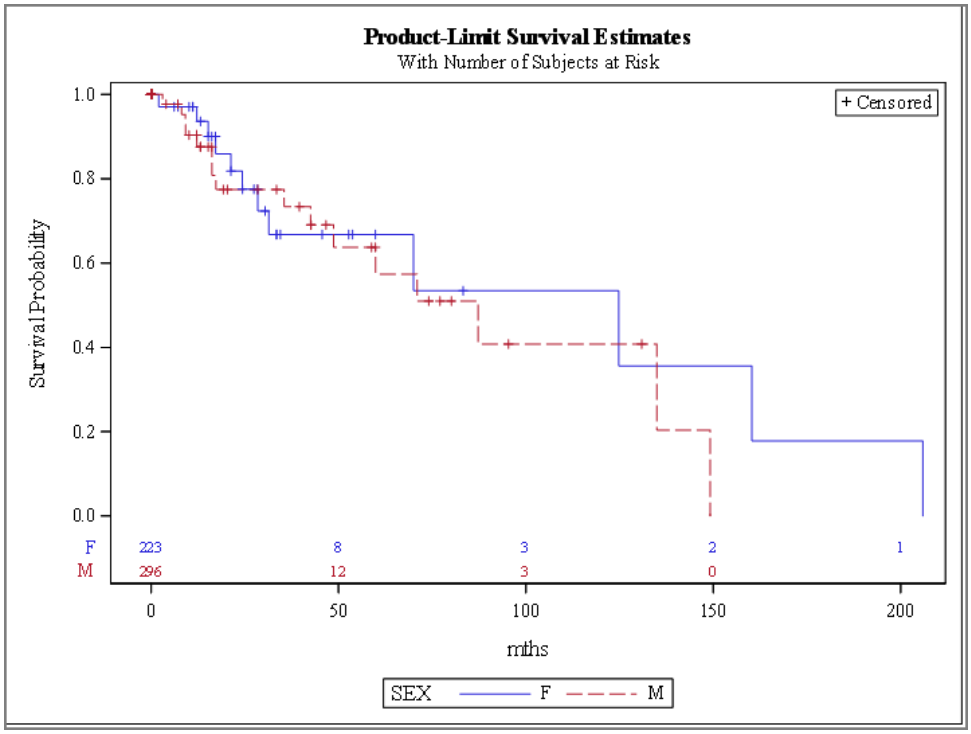


Figure 5.12: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against Site of Initial PMD lesion.

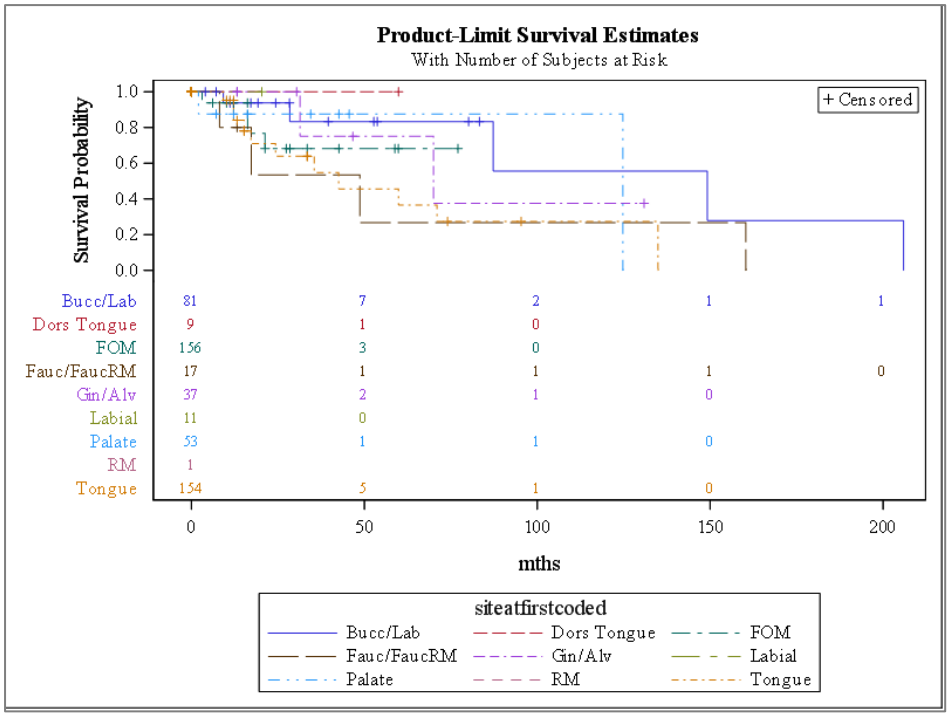


Figure 5.13: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against Clinical Appearance of Initial PMD lesion: Erythroleukoplakia (ELK) 71.0, 95%CI 59.9-160.3; Erythroplakia (EK) 87.3, 95%CI 8.1-87.3; Leukoplakia (LK) 124.8, 95%CI 42.6-149.2; p=0.55.

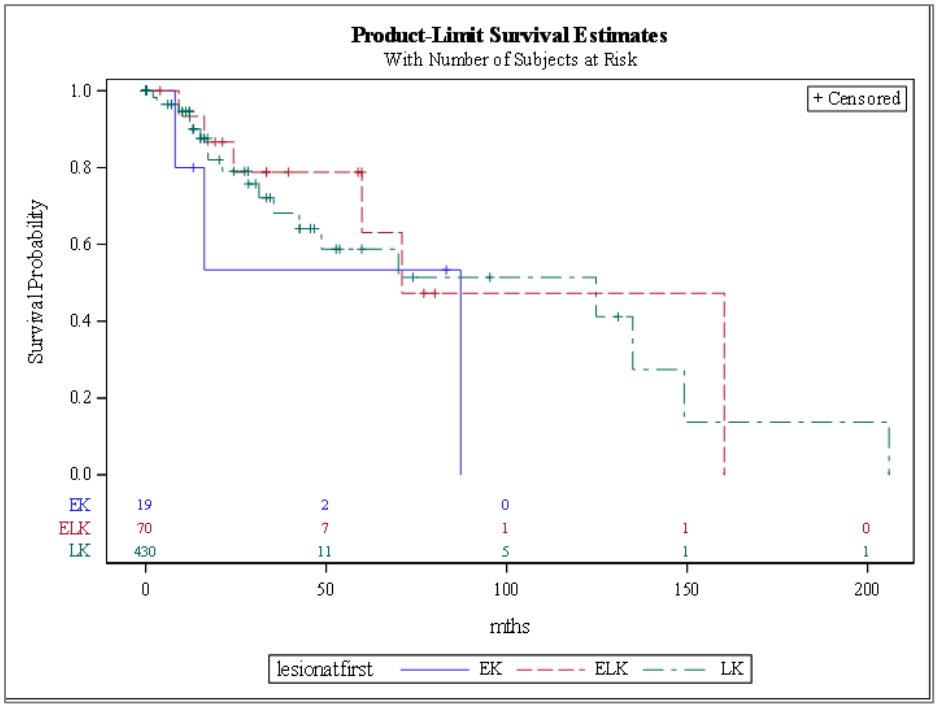


Figure 5.14: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against WHO Dysplasia Grading (most significant from combined incision/excision data): Mild 42.6, 95%CI 28.4-NA; Moderate 70.0, 95%CI 15.2-205.9; Severe 71.0, 95%CI 35.5-149.2; None 87.3, 95%CI 48.7-160.3; p=0.96.

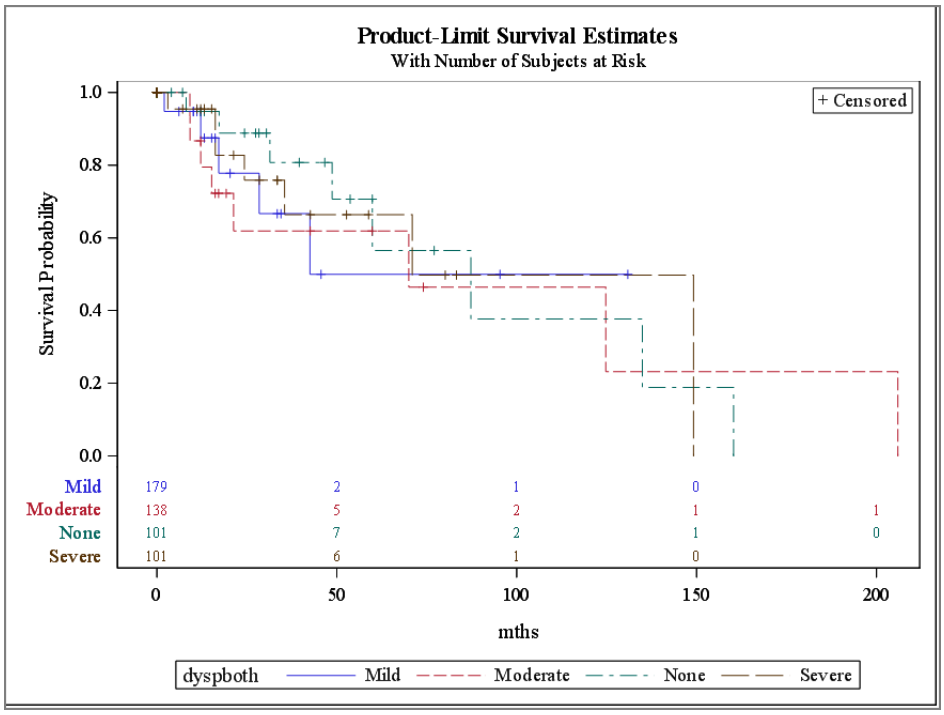


Figure 5.15: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against Binary Dysplasia Grading (most significant from combined incision/excision data): Low Grade (Mild/Mod) 70.0, 95%CI 28.4-205.9; High Grade (Severe) 71.0, 95%CI 35.5-149.2; None 87.3, 95%CI 48.7-160.3; p=0.86.

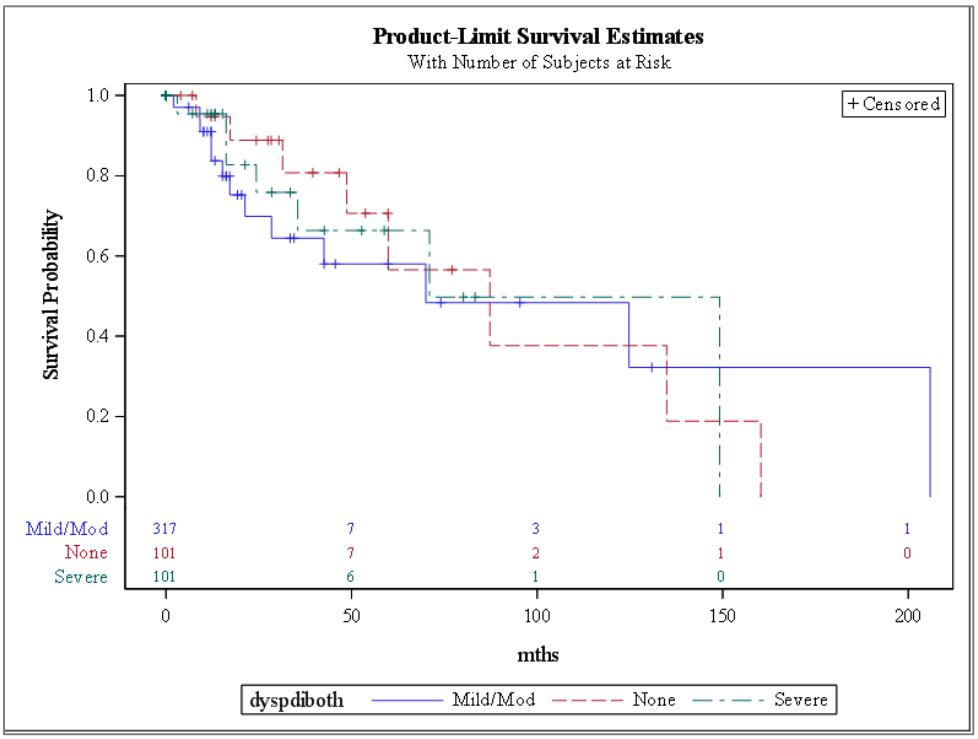


Figure 5.16: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against the histopathological identification of Proliferative Verrucous Leukoplakia (PVL).

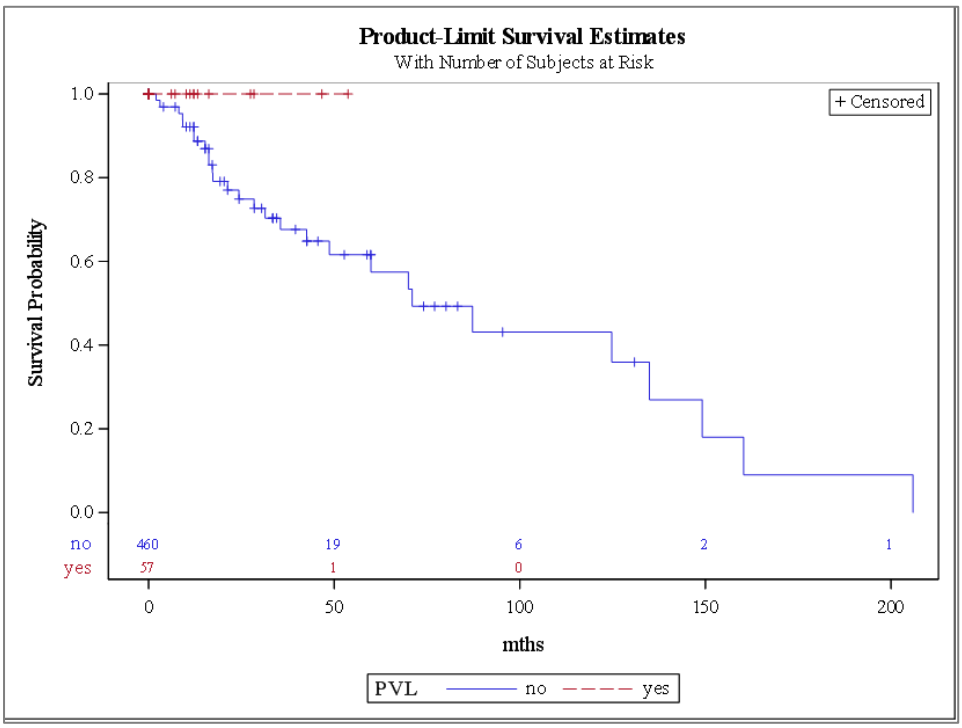
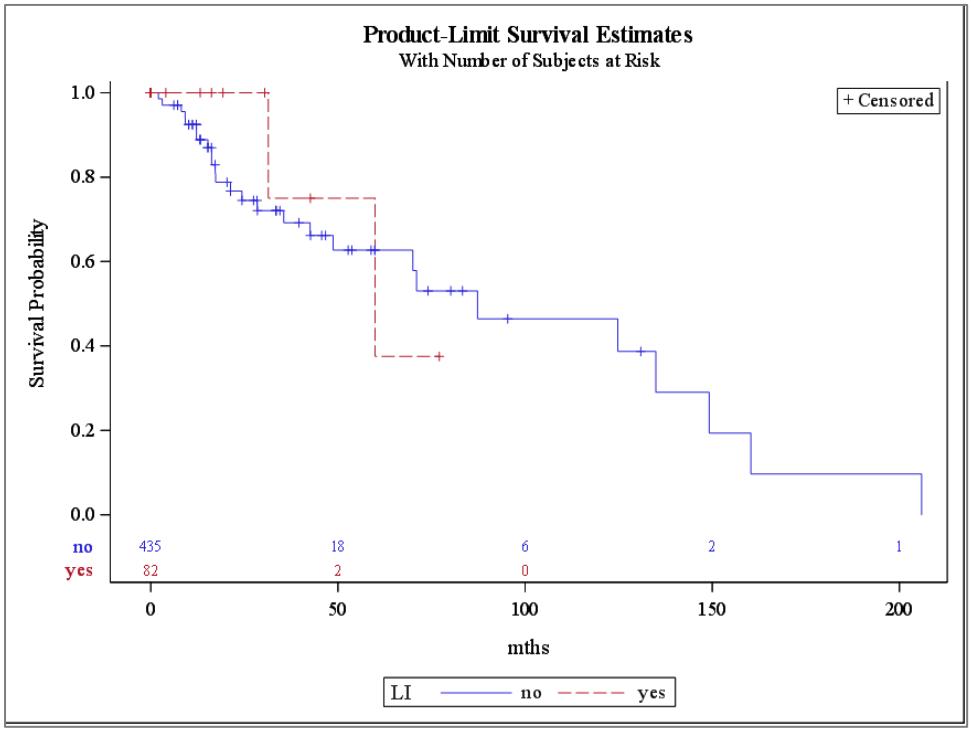


Figure 5.17: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) against the histopathological identification of Lichenoid Inflammation (LI): LI 59.9, 95% CI 31.4-NA; No LI 87.3, 95% CI 48.7-149.2; p=0.70.



5.4.10. Comparative Analyses of Clinical Outcome Categories. A number of comparative analyses were carried out utilising the defined clinical outcome categories of: Disease Free, Further Disease which progressed to Disease Free status following further intervention (Further/DF), Further PMD Disease which persisted despite intervention (Further/Persistent) and Malignant Transformation (MT).

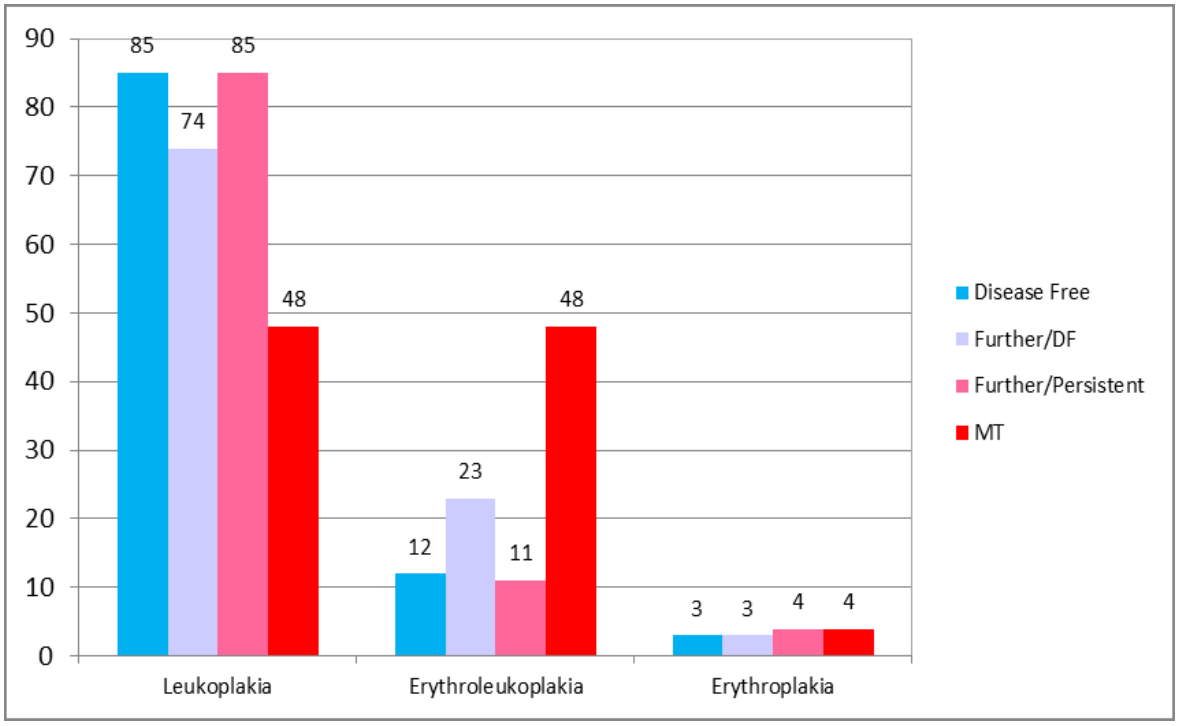
Table 5.32 lists the clinical appearance of PMD lesions seen in each clinical outcome category whilst Figure 5.18 illustrates, to facilitate a direct comparison, the percentage of lesions within each category plotted against their presenting clinical appearance. A significant difference in clinical outcome was seen between lesions with varying clinical appearance, most notably the high percentage of erythroleukoplakic lesions undergoing malignant transformation ($p<0.0001$; Fisher's exact test).

TABLE 5.32: CLINICAL APPEARANCE OF PMD LESIONS IN EACH CLINICAL OUTCOME CATEGORY

	Disease Free	**Further / DF**	**Further/ Persistent**	**Malignant Transformation**
Leukoplakia	341 (85%)	25 (74%)	45 (85%)	48 (48%)
Erythroleukoplakia	50 (12%)	8 (23%)	6 (11%)	47 (48%)
Erythroplakia	13 (3%)	1 (3%)	2 (4%)	4 (4%)
Totals	404 (100%)	34 (100%)	53 (100%)	99 (100%)

Fisher's exact test p<0.0001

Figure 5.18: Clinical Appearance of PMD Lesions versus Outcome, plotting the percentage of leukoplakia, erythroleukoplakia and erythroplakia lesions against clinical outcome categories, comprising *DF* disease free, *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



In Table 5.33, and subsequently illustrated in Figure 5.19, the change in PMD appearance between initial presenting lesion and further PMD disease is shown for each clinical outcome category (excepting disease free cases). The same clinical appearance was most commonly seen in the Further/Persistent Disease group ($p<0.0001$; Chi-squared test).

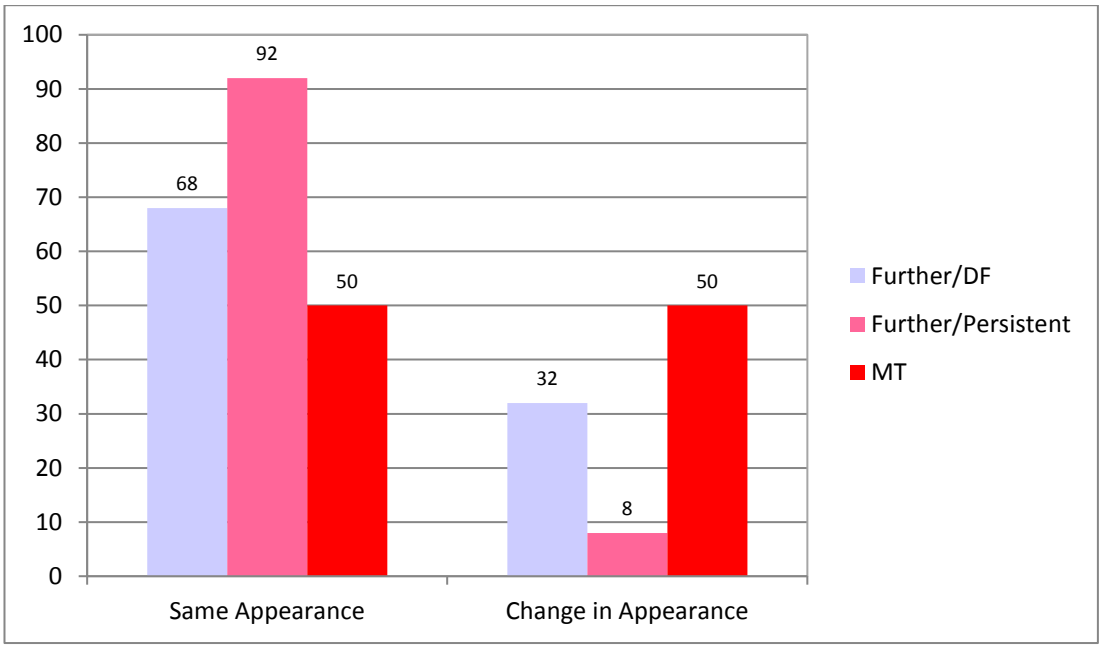
TABLE 5.33: CLINICAL APPEARANCE OF PMD LESIONS IN EACH CLINICAL OUTCOME CATEGORY FOLLOWING INTERVENTIONAL LASER SURGERY

	Further / DF	Further / Persistent	Malignant Transformation
Same Appearance	23 (68%)	49 (92%)	14 (50%)
Change in Appearance	11 (32%)	4 (8%)	14 (50%)
Totals	34 (100%)	53 (100%)	28* (100%)

**Only Transforming SCC Cases Included*

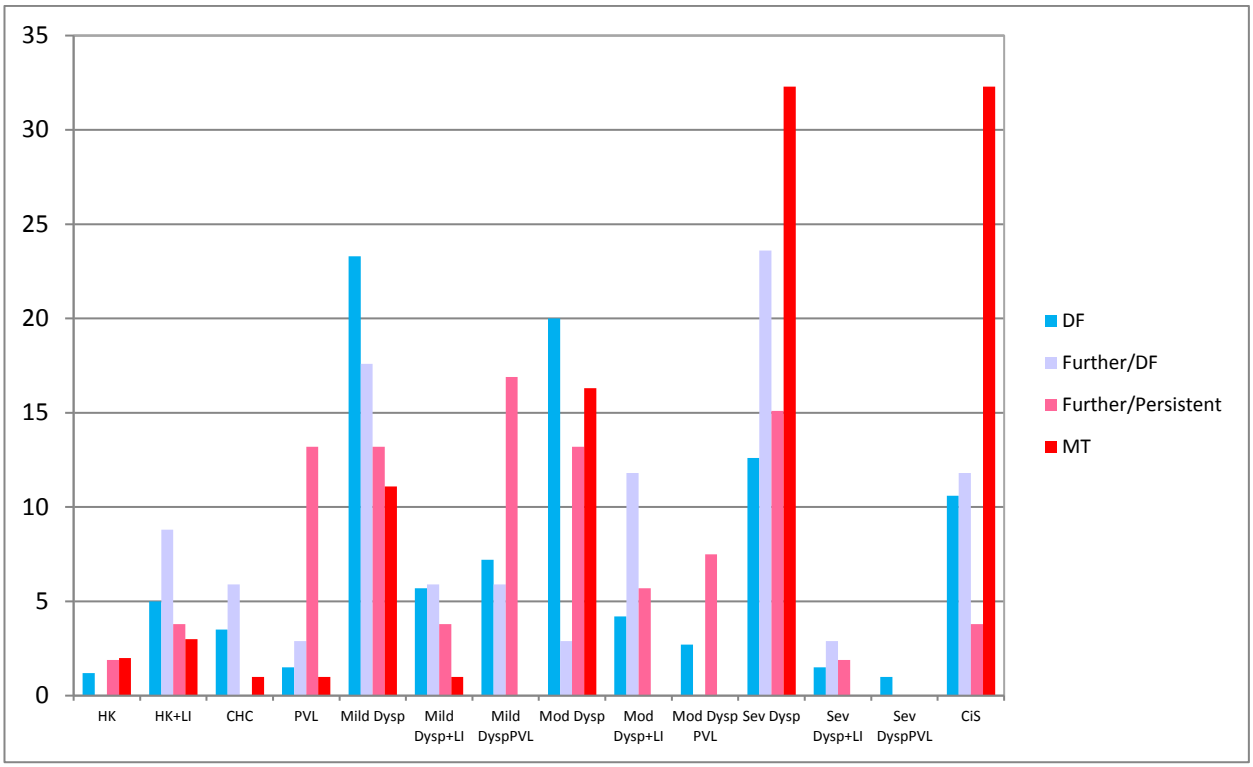
Chi-squared test p<0.0001

Figure 5.19: Change in Appearance of PMD Lesions following Interventional Laser Surgery versus Outcome, plotting the percentage of same or changed appearance against clinical outcome for the categories of *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



In Figure 5.20, the percentage of PMD lesions exhibiting each clinical outcome is plotted against their most significant initial histopathological diagnosis; malignant transformation is most frequently seen in lesions that exhibited severe dysplasia or carcinoma-in-situ, as originally illustrated in Figure 5.4.

Figure 5.20: Histopathology Diagnoses for PMD Lesions versus Outcome, plotting the percentage of each diagnosis against clinical outcome categories, comprising *DF* disease free, *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



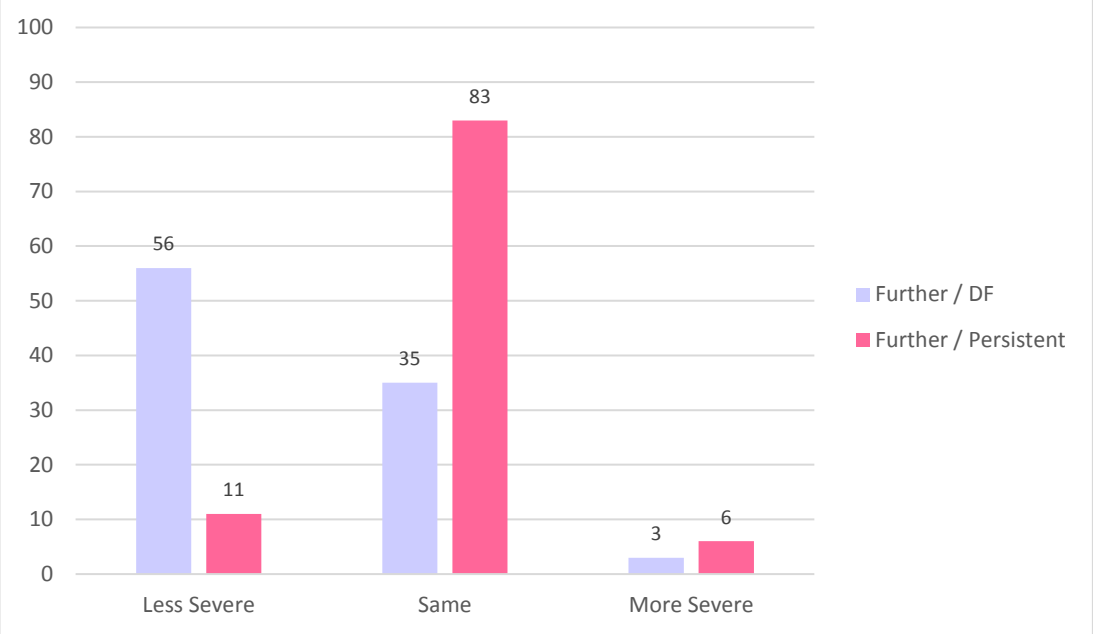
In Table 5.34 and in Figure 5.21, the change in severity of histopathological grading between initial and subsequent PMD lesion biopsy is analysed against clinical outcome, suggesting that PMD lesions which persist were more likely to retain their original histopathological character, whilst the pathological appearance of subsequent lesions was likely to be less severe in the Further/Disease Free category (p=0.013; Fisher's exact test).

TABLE 5.34: CHANGE IN SEVERITY OF HISTOPATHOLOGY DIAGNOSES BETWEEN PRESENTING AND FURTHER PMD LESIONS FOLLOWING INTERVENTIONAL LASER SURGERY

	Further / DF	Further / Persistent
Less Severe	12 (56%)	6 (11%)
Same	19 (35%)	44 (83%)
More Severe	3 (9%)	3 (6%)
Totals	34 (100%)	53 (100%)

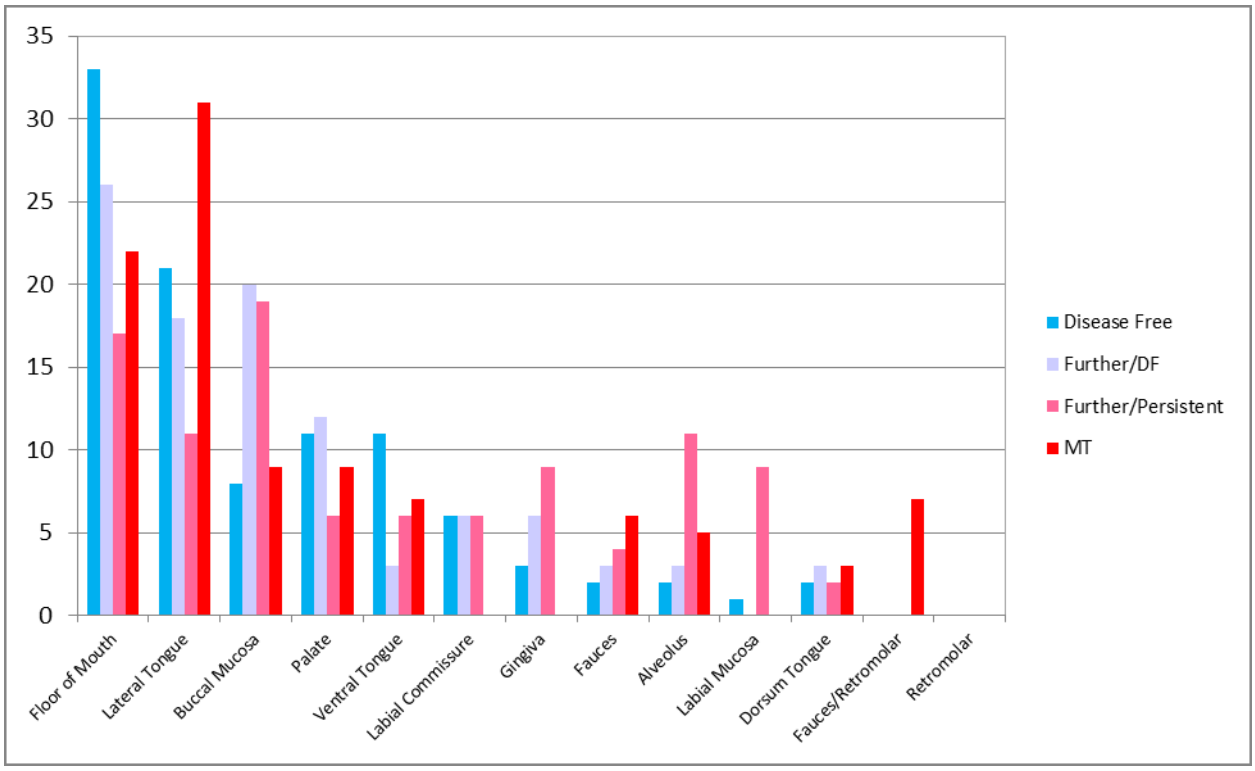
Fisher's exact test p=0.013

Figure 5.21: Change in Histopathology Diagnoses between Presenting PMD Lesion and Further Lesions versus Outcome, plotting the percentage of less severe, same and more severe histopathological diagnosis against the clinical outcome categories of *Further/DF* whereby further PMD disease resolved to disease free status, and *Further / Persistent* when PMD lesions persisted.



By plotting anatomical location against outcome, Figure 5.22 confirms that malignant transformation is more commonly seen in PMD lesions arising at lateral tongue and floor of mouth sites, confirming data initially presented in Figure 5.7.

Figure 5.22: Anatomical Location of PMD Lesions versus Outcome, plotting the percentage of lesions seen at each oral site against clinical outcome categories, comprising *DF* disease free, *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



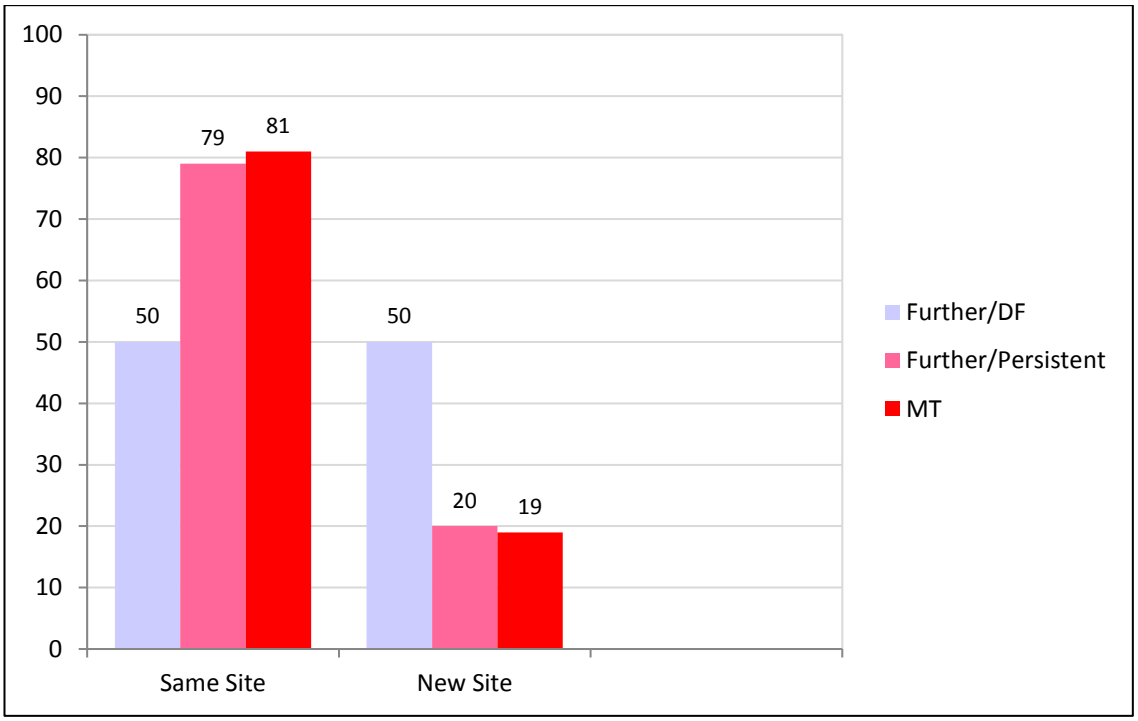
In terms of change in anatomical site location, Table 5.35 and Figure 5.23 show that Further/Persistent Disease and Malignant Transformation occurred more frequently at the same site as the initial presenting lesions (p=0.0003; Chi-squared test), whereas this relationship was less clear for Further/Disease Free status.

TABLE 5.35: ANATOMICAL LOCATION OF PMD LESIONS IN EACH CLINICAL OUTCOME CATEGORY FOLLOWING INTERVENTIONAL LASER SURGERY

	Further / DF	Further / Persistent	Malignant Transformation
Same Site	17 (50%)	42 (79%)	80 (81%)
New Site	17 (50%)	11 (21%)	19 (19%)
Totals	34 (100%)	53 (100%)	99 (100%)

Chi-squared test p=0.0003

Figure 5.23: Change in Anatomical Location between Presenting PMD Lesion and Further Lesions versus Outcome, plotting the percentage of same site and new site PMD disease against the clinical outcome categories of *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



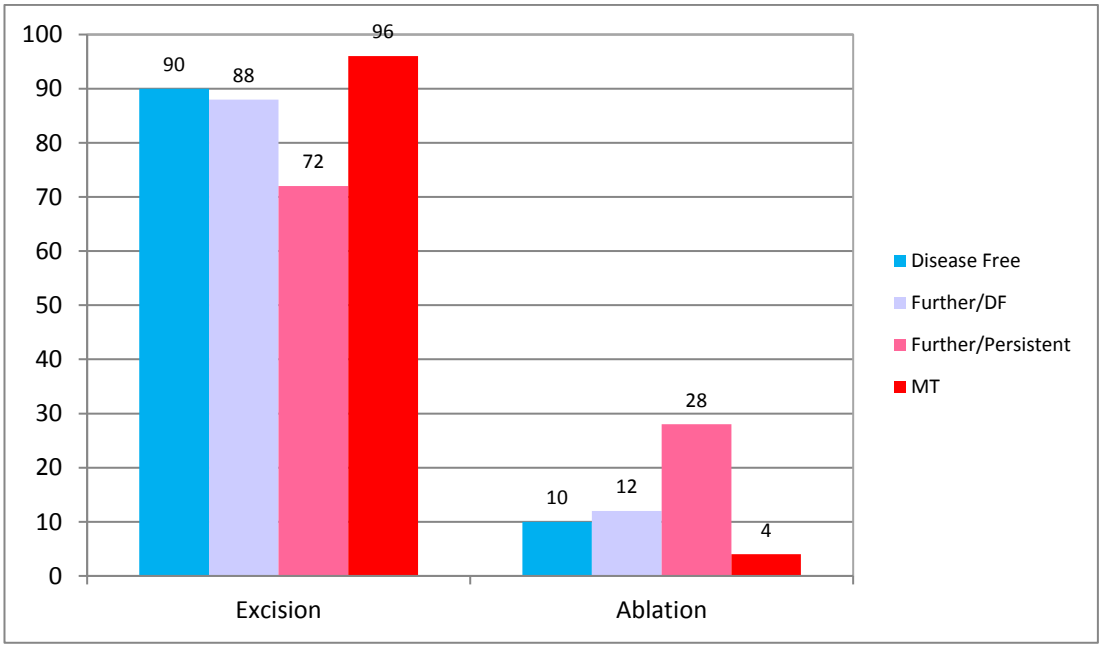
Regarding the method of interventional laser management, Table 5.36 and Figure 5.24 demonstrate clinical outcomes seen following either laser excision or ablation techniques, confirming significant difference with ablation associated with a higher number of Further/Persistent PMD disease cases ($p<0.0001$; Chi-squared test).

TABLE 5.36: CLINICAL OUTCOME RESULTS IN RELATION TO INTERVENTIONAL LASER SURGERY TECHNIQUE (EXCISION vs ABLATION)

	Disease Free	Further / DF	Further / Persistent	Malignant Transformation
Excision	363 (90%)	30 (88%)	38 (72%)	95 (96%)
Ablation	41 (10%)	4 (12%)	15 (28%)	4 (4%)
Totals	404 (100%)	34 (100%)	53 (100%)	99 (100%)

Chi-squared test p<0.0001

Figure 5.24: Interventional Laser Surgery Technique (Excision or Ablation) versus Outcome, plotting the percentage of each clinical outcome category against surgical technique, comprising *DF* disease free, *Further/DF* whereby further PMD disease resolved to disease free status, *Further / Persistent* when PMD lesions persisted, and *MT* malignant transformation.



5.5 Discussion

5.5.1. Introduction. This data set of 590 PMD patients, undergoing a standardised and coordinated treatment intervention by a single surgeon, is the largest cohort of its kind ever studied and as such offers unparalleled insight into the natural history of oral potentially malignant disease in the North-East of England. The study also provides detailed clinical outcome data recorded over one of the longest ever follow-up periods, 19 years, with a mean patient follow-up of 7.3 years.

5.5.2. Patient Demographics. The age and sex demographics of the study population appear consistent with previous Newcastle patient cohort studies, confirming a median patient age of 60 years and, with 59% of cases male and 41% female, a 1.4:1 male to female ratio; these data are consistent with several recent PMD population studies (Cowan et al 2001, Jaber et al 2003, Jerjes et al 2012a, Dost et al 2013 & 2014, Watabe et al 2015). No significant relationships between patient age or sex and potentially malignant disease presentation or clinical outcome were characterised in this study which is similar to our observations from all previous analyses (Thomson & Wylie 2002, Hamadah & Thomson 2009, Diajil et al 2013); patient numbers, although large in terms of PMD studies, are probably too limited to be able to determine significant demographic differences. As in previously documented reports, the vast majority of PMD patients in this study regularly smoked tobacco (87%) and drank alcohol (84%), confirming these as the most significant aetiological factors in this Northern England population.

5.5.3. Clinico-Pathological Features. Consistent with previously published Newcastle data, the vast majority of oral lesions in this study (79%) presented as leukoplakia, with the floor of mouth and ventro-lateral tongue sites most commonly affected (61%); these observations are highly consistent with many other previously published studies (Schepman et al 1998, Warnakulasuriya et al 2011, Ho et al 2012, Jerjes et al 2012a,

Graveland et al 2013, Dost et al 2014). We have previously characterised increased epithelial cell proliferative activity within floor of mouth and ventral tongue sites, and it may well be that these oral regions actually exhibit an underlying predisposition to carcinogenic influence, particularly as increasing cell dysregulation appears to be a key factor driving oral carcinogenesis (Liu et al 1998, Thomson et al 1999a & 1999b, 2001, 2002, Cruz et al 2002, Thomson et al 2006 & 2008).

Histopathological diagnoses for all 590 patients in this study were provided by 4 specialist oral pathologists, based in the Pathology Department at the Royal Victoria Infirmary in Newcastle, who worked throughout the study period using agreed WHO diagnostic standards with appropriate peer review and consensus grading. The majority of oral lesions in the study exhibited significant histopathological abnormality, with 88.5% showing dysplasia or carcinoma-in-situ; this is also similar to our previous studies and distinguishes this patient data set from many others in the literature in which disparate types of lesions, many non-dysplastic in nature, are included in retrospective analyses (Thomson 2012d). Re-examination of tissue specimens in a formal, research-orientated approach was not undertaken in this MD study as it was felt such re-calibrated data would not accurately reflect the 'real-world' nature of the PMD diagnosis and management protocol that the 590 cases had undergone. Whilst Dost et al (2014) have also commented on this issue in relation to oral epithelial dysplasia research, Speight et al (2015) have more recently reported upon a multi-stage histopathology review and adjudication process which they hope may form the basis of a 'gold standard' for future oral potentially malignant disorder research.

The extensive PMD data set in this study not only benefits from coordinated clinical recording and consistent 'real-world' histopathological diagnoses by experienced oral pathologists, but is also one of the largest and best defined series of oral dysplastic lesions in the current literature. Table 5.37 summarises and compares patient demography and salient clinico-pathological features from this current study with 4 previous Newcastle patient cohort studies. Whilst most features are consistent through the years,

there does appear to be a slight increase in the number of female patients affected by PMD disease in the present study. This latter observation is consistent with many recent reports suggesting an increase in oral carcinogenesis in female patients, possibly due to a rise in tobacco and alcohol consumption in younger females (Warnakulasuriya 2009, 2010).

TABLE 5.37: COMPARATIVE PATIENT DEMOGRAPHIC AND CLINICO-PATHOLOGICAL DATA FOR NEWCASTLE PMD PATIENT COHORT STUDIES (2002-2016)

		Thomson & Wylie (2002)	Thomson et al (2008)	Hamadah & Thomson (2009)	Diajil et al (2013)	Thomson (2016)
No. of Patients		57	40	78	100	590
M:F Ratio		1.85:1	2.3:1	1.9:1	2.1:1	1.4:1
Mean Age (Yrs)		59.9	59.7	57.8	58.5	60
Clinical Lesion (%)	Leukoplakia	69	65	68	78	79
	Erythroleukoplakia	28	23	27	16	17
	Erythroplakia	3	7	5	8	4
Floor of Mouth / Ventro-Lateral Tongue Site (%)		68	78	89	79	61

An interesting observation, illustrated in Figure 5.2, was the trend for increased recognition of lesions exhibiting lichenoid inflammation or proliferative verrucous features on histopathological examination during the later years of the study. It is likely that this is due to an increasing awareness amongst oral pathologists not only of the potential significance of lichenoid lesions and the risk of a poorer clinical outcome (as specifically reported

upon in Publication 2.4 of this thesis) but also greater recognition of the relevance of persistent, multi-focal mucosal disorders such as proliferative verrucous leukoplakia (PVL) which are increasingly believed to exhibit a high risk of malignant transformation (Bagan et al 2010a, 2011). Interestingly, comparison of Figure 5.2 with Figure 4.5 confirms a similar increase in laser ablation techniques over the same time period, which parallels the increase in PVL lesions seen primarily affecting keratinised gingiva and alveolar sites.

The prognostic significance of oral lesions exhibiting lichenoid inflammatory features has, of course, been debated for many years and remains controversial, although in this study patients whose lesions showed lichenoid inflammation were less likely to achieve Disease Free status, and there is little doubt that in clinical practice identification of isolated erythroleukoplakic lesions showing lichenoid features and arising at sites such as the ventro-lateral tongue are increasingly regarded as being at 'high risk' for malignant transformation (Thomson 2012e, Farah et al 2014). Dost et al (2013) observed lichenoid features in 25 out of 124 dysplastic oral lesions (20%); this is higher than the 11.5% (60 lichenoid inflammatory lesions out of 522 dysplasias) seen in this study, however. Some authors have coined the term 'lichenoid dysplasia' for such lesions, and emphasised their high risk of progression to carcinoma, although the term is not universally applied (Krutchkoff & Eisenberg 1985, Lovas et al 1989, Speight 2007, Dost et al 2013, Patil et al 2014). Whilst oral lichenoid lesions have not been routinely followed up continuously, some authors have recommended this practice to specifically monitor for early cancerous change (Xue et al 2005, Al Hashimi et al 2007, Greaney et al 2014).

Traditionally, diagnoses of proliferative verrucous leukoplakia (PVL) have generally been made late during the course of PMD presentation once progressive spread to different oral sites, high recurrence rates following treatment intervention and malignant transformation all become apparent. Increasingly, specialist oral pathologists have attempted earlier and more objective diagnoses for verrucous hyperplastic lesions considered to be part

of the PVL spectrum which almost certainly accounts for the increased frequency of the diagnosis during the latter years of this study (Speight 2007, Cerero-Lapiedra et al 2010). Gouvea et al (2013) usefully emphasised salient criteria to support contemporary PVL diagnoses including: females older than 50 years with no active tobacco or alcohol misuse, multiple-site leukoplakic lesions, and progressive clinical and histopathological features confirmed during follow-up. Whilst these authors quoted an approximate UK PVL prevalence of 0.1% (1 PVL for every 1000 leukoplakias), 74 out of the 590 PMD lesions in this MD study (12.5%) were shown to exhibit features of PVL (Table 5.3) suggesting a much higher disease presence.

Histopathologically, PVL has classically been described as exhibiting a continuum of morphological change, passing through an initial phase of hyperkeratosis without dysplasia, followed by verrucous hyperplasia leading on to verrucous carcinoma and invasive squamous carcinoma (Cerero-Lapiedra et al 2010). Complicating the early phase of lesion development further, however, is the recognition that significant lymphocytic infiltration may be identified in the immediate sub-epithelial region effectively mimicking the appearance of oral lichenoid lesions (Issrani et al 2013); these latter observations may have particular relevance for the study data reported in Publication 2.4.

Whilst it remains to be seen exactly how far such histopathology diagnoses will equate with PMD lesion behaviour long-term, clinicians specialising in potentially malignant disease must for now remain highly vigilant for signs and symptoms of putative PVL disease, liaising closely with pathology colleagues in agreeing diagnostic criteria which must be appropriately tailored to individual, presenting cases (Gouvea et al 2013).

Chronic hyperplastic candidosis (CHC), sometimes termed candidal leukoplakia, is a specific potentially malignant variant of oral candida infection that may present as leukoplakia on the labial commissures of tobacco smokers; it is unclear whether candida initiates dysplastic change or is merely a ‘passenger’ within the abnormal epithelium (Sitheeque &

Samaranayake 2003). Whilst there is no overall consensus on management, the 17 cases identified in this MD study were initially treated with systemic anti-fungal treatment and smoking cessation advice prior to CO_2 laser treatment of their persisting lesions which successfully rendered 16 free from disease. Interestingly, 1 case arising on buccal mucosa exhibited unexpected squamous carcinoma which was diagnosed only following laser excision.

Formal re-assessment of original histopathology specimens for research calibration did not form part of the methodology of this MD thesis, but there is little doubt that review of PMD cases with known unfavourable clinical outcome data, especially those exhibiting lichenoid inflammatory change and PVL features in archived biopsy specimens, could well contribute to useful, future clinico-pathological characterisation of PMD lesions and perhaps an improved understanding of their overall natural history.

5.5.4. Laser Excision Histopathological Data. The structured treatment intervention applied throughout the study period facilitated a unique, direct comparison of 609 histopathological diagnoses from initial, incision biopsy samples with their 'whole lesion' laser excision counterparts. An important hypothesis influencing the Newcastle interventional treatment protocol was, of course, that incision biopsy data alone cannot accurately represent the true nature of oral potentially malignant lesions. Agreement between incision and excision diagnoses was seen in only 50% of samples in this study, with 36% having to be subsequently 'up-graded' in severity once 'whole lesion' specimens were also examined microscopically; Figure 5.3.

Kappa agreement between incision and excision biopsy data, both using traditional WHO dysplasia grading and an arbitrary 'binary' system was only deemed moderate, although overall histopathology agreement for all diagnostic samples appeared slightly improved when 'high-grade' and 'low-grade' classifications were utilised. Formal testing of the effectiveness of different dysplasia grading systems was not, of course, part of the remit of this investigation.

Perhaps of most clinical significance, however, was the poor specificity (16.3%) of incision biopsy techniques to diagnose squamous carcinoma in oral potentially malignant lesions when directly compared with laser excision biopsy (kappa agreement only 0.25). As the majority of laser treatments in this study were all carried out within 6 to 12 weeks of initial biopsy, disease progression is not likely to be a major influence on any disparity between tissue samples (Lumerman et al 1995, Warnakulasuriya et al 2011, Diajil et al 2014). Rather, these differences most likely reflect a more specific inadequacy of undertaking limited, incision biopsy sampling of oral lesions, which is especially pertinent for potentially malignant disorder cases presenting with larger, more widespread and multi-focal mucosal disease; the latter clinical presentation is known to affect up to 25% of Newcastle PMD patients (Hamadah et al 2010).

Table 5.38 compares the MD study data with 2 earlier Newcastle laser studies in which comparison of incision and excision biopsies were also carried out. Consistent diagnoses were seen in 50 to 55% of cases, but more severe dysplasia was seen in 11 to 29% of excision specimens and, perhaps of most significance, squamous cell carcinoma was identified in a further 9 to 16%. In 7 to 25% of cases, excision biopsy specimens showed less severe dysplasia than initial biopsy, but this is of no real clinical significance as such lesions always retain their most significant histopathology diagnosis in practice and should never be ‘down-graded’.

TABLE 5.38: COMPARISON BETWEEN LASER EXCISION HISTOPATHOLOGY DIAGNOSES AND INITIAL INCISION BIOPSY DATA IN NEWCASTLE PMD PATIENT COHORT STUDIES (2002-2016)

		Thomson & Wylie (2002)		**Goodson & Thomson (2011)**		**Thomson (2016)**	
		No.	*%*	No.	%	No.	%
Direct Comparisons		*55*	*100*	169	*100*	609	*100*
Dysplasia	Less Severe	14	*25*	11	*7*	82	*14*
	Same	30	*55*	94	*55*	307	*50*
	More Severe	6	*11*	49	*29*	122	*20*
SCC		5	*9*	15	*9*	98	*16*

van der Waal (2009a) emphasised the important distinction between incision biopsy diagnoses, which should only be considered provisional in nature, and the more definitive diagnoses achieved via whole lesion inspection; the results from the 609 specimens examined in this study strongly support this viewpoint, and concur with the arguments presented in sections 1.6.1 and 1.6.2 of this thesis. Dost et al (2014) have recently recommended that all potentially malignant oral lesions exhibiting dysplasia should receive definitive treatment by whole lesion excision.

As discussed in section 1.6.3, thermal cytological artefacts following CO_2 laser excision biopsies have been suggested as a limitation of such treatment intervention (Seoane et al 2010), but their presence or absence did not detract from full and accurate histopathology assessment and diagnosis for the 609 excisions specimens analysed in this study by specialist oral pathologists in Newcastle.

5.5.5. Clinical Outcome. Long-term cohort studies such as this one facilitate detailed analysis and stratification of clinical outcome data, and the outcome categories applied to patients in this study were refined to specifically reflect important, distinct clinical outcomes for treated PMD cases. In this study, nearly three-quarters of patients (74.2%) were recorded as PMD Disease Free at the end of study census date, confirming considerable efficacy of laser intervention as a treatment modality. This is especially pertinent because 88.5% of lesions were treated for significant dysplasia or carcinoma-in-situ, and these results compare favourably with previous outcome data from our studies originally summarised in Table 1.5. In terms of patient profiling, Disease Free patients tended to be of a younger age and on histopathological examination exhibited mild or moderate dysplasia without the presence of lichenoid inflammatory features in their biopsy specimens; section 5.4.6.

It is difficult to meaningfully compare treatment outcomes from this MD study group with other published data due to substantive differences in diagnostic and clinical decision making processes, varying types of lesions treated, inconsistent surgical techniques and lack of agreed clinical outcome definitions in most papers in the current literature (Shiu & Chen 2003, Thomson 2012d). Yang et al (2015) recently commented, not entirely helpfully, that making any comparison between PMD treatment studies is probably impossible. Nonetheless, data from 6 recent, comparable CO_2 laser treatment studies is tabulated and an attempted comparison with this MD study presented in Table 5.39.

TABLE 5.39: COMPARATIVE CLINICAL OUTCOME DATA FOR CO_2 LASER TREATMENT STUDIES

	van der Hem (2005)	Yang et al (2011)	Jerjes et al (2012a)	Del Corso et al (2015)	Matsumoto et al (2015)	Mogedas-Vegara et al (2015)	Thomson (2016)
Treated Patients (No)	282	114	77	30	38	65	590
Follow-Up (Mean Years)	4.3	3.4	6.4	5	0.5	1.25	7.3
Disease Free	89%	71.1%	70.1%	86.7%	81.6%	50.8%	74.2%
Further Disease	9.9%	17.5%	29.9%	13.3%	18.4%	33.8%	15.4%
Development of SCC	1.1%	11.4%	10.4%	0%	0%	15.4%	16.8%

Whilst the data from this MD study cohort comprises by far the largest number of treated patients (590) and the longest mean follow-up period (7.3 years), the overall pattern for clinical outcome listed in Table 5.39 appears quite similar between studies. Disease Free outcomes are seen in 50.8 to 89% of cases (mean calculated as 74.8%), whilst further PMD disease affected between 9.9 and 33.8% (with a mean of 19.7%).

The specific follow-up data collected during the MD study allowed an additional distinction to be made between patients ultimately rendered Disease Free following further potentially malignant disease presentation and subsequent repeat treatment (34 or 5.8%), and those whose disease persisted despite repeated intervention (53 or 9%). The characteristics of these distinct further disease outcome categories have been analysed in sections 5.4.7 and 5.4.8, and summarised in Table 5.24. Although primarily statistically non-significant, probably due to the low sample size, patients who exhibited Further/Persistent PMD disease (that is, disease arising at the same anatomical site, and with consistent clinical and histopathological features) tended to be slightly older, presented most commonly with lesions

on the gingiva, alveolus and labial mucosa, often exhibiting clinico-pathological features consistent with PVL and were more likely to have been treated by ablation techniques rather than surgical excision (as summarised in Table 5.36 and Figure 5.24). Other workers have also noted high disease recurrence following PVL treatment; Bagan et al (2011), for example, reported an 85% rate of PVL recurrence following both laser and surgical intervention. In contradistinction, patients in the Further/Disease Free category were younger, presented with new lesions at different oral sites, usually with less severe dysplastic features and responded well to multiple laser excision treatments; the latter observation, interestingly, being the only statistically significant one ($p<0.0001$; Chi-squared test).

Jerjes et al (2012a) followed 77 PMD patients after CO_2 laser surgery and distinguished clinical outcomes that included complete response, partial response, stable disease, progressive disease, recurrence and malignant transformation but as these categories were used differently between initial treatment and subsequent 3, 5-year and final outcome assessments it is difficult to make a direct comparison with the data analysed in this thesis. Jerjes et al (2012a) did observe, however, a significantly increased risk for recurrent PMD disease and malignant transformation to affect erythroplakic and non-homogeneous leukoplakic lesions, and to arise more often in heavy smokers and heavy alcohol drinkers.

Chiesa et al (1993) reported that following successful primary treatment intervention, 18.5% of oral leukoplakia patients exhibited local disease recurrence, 16.2% developed new-site leukoplakia and 6.6% developed carcinoma. Primarily resulting from field change carcinogenesis, environmental factors may still influence dysplastic and neoplastic change in such patients. Wan et al (2014) reviewed 6 papers in which persistent or further PMD disease was identified following treatment and reported a frequency for new lesions (principally leukoplakia) to affect between 6.3% and 83.3% of cases.

Malignant transformation rates for PMDs vary worldwide, of course, with quoted values ranging between 0.1 to 40% making it extremely difficult to

effectively counsel individual patients. Such data are probably the most difficult to interpret in the literature and in Table 5.39 alone, rates are seen to vary from 0 to 16.8% (mean 7.45%). However, close inspection of the zero transformation results reported by Del Corso et al (2015) and Matsumoto et al (2015) is warranted because only small numbers of PMD lesions were actually treated in these studies, 40 to 60% of lesions were non-dysplastic and, in the Matsumoto et al (2015) study, only a limited follow-up of 6 months post-treatment was carried out. In contrast, 88.5% of lesions in this much larger MD study exhibited significant dysplasia, most carcinomas (71 or 12%) were diagnosed fortuitously upon initial laser excision and, as we have previously demonstrated, the incidence of further PMD disease and malignant transformation are both known to increase with length of follow-up, which was longest in this study at 7.3 years (Diajil et al 2013, Wan et al 2014).

The median transformation time for the 28 cases that developed cancer in this MD study was 87.3 months, which emphasises the importance of long-term clinic follow-up for these cases. The difficulty remains, however, how to identify or predict those patients at particular risk of such transformation. Review of the malignant transformation data from this study suggests that a clear and important distinction should be made between the identification of pre-existing but unknown foci of squamous cell carcinoma in oral mucosal lesions and the development of carcinoma in a patient who has previously been diagnosed and treated for a potentially malignant lesion. In our 590 patient study the former clearly predominated (71 cases) with only 28 developing carcinoma post-treatment. Clinico-pathological features that were associated with malignant transformation included erythroleukoplakic lesions, the presence of severe dysplasia or carcinoma-in-situ in initial biopsies and floor of mouth and lateral tongue sites of origin; these observations are consistent with previously reported data (Napier & Speight 2008), although other authors have not found clinical or pathological observations to reliably or consistently correlate with malignant transformation risk (Arduino et al 2009, Watabe et al 2015). We have shown in a number of patient cohort studies that whilst intervention may reduce the risk of same-site malignant

transformation in treated cases, there remains the risk of field change cancerization and new site disease (Thomson & Wylie 2002, Hamadah & Thomson 2009, Thomson 2012e, Diajil et al 2013, Thomson 2014).

Clearly, the emphasis during PMD treatment must be to identify those cases in which the risk of dysplastic disease progression and malignant transformation are at their highest level, and then to intervene definitively in the shortest period of time possible, as reviewed by Diajil et al (2014). The comparative analyses carried out between the different clinical outcome categories in Section 5.4.10 has provided insight into the varying clinical presentation of PMD and the importance of monitoring for change during patient follow-up. Ultimately, however, despite the ability of clinicians to identify potentially malignant oral lesions, there are very few clinico-pathological features that consistently characterise distinct PMD lesion behaviours, and accurate prediction of all clinical outcome data still remains frustratingly elusive in contemporary clinical practice (Lee et al 2000, Speight 2007, Thomson 2012d).

5.5.6. Limitations of the Study. The study reported in this chapter is inevitably limited by the realization it is not a prospective, randomised controlled trial, nor is it multi-centre in its organisation. Similarly, it is important to recognise the inherent allocation bias affecting both patient recruitment and treatment intervention, which are firmly based on the author's preferred management protocol. The latter, of course, may weaken the establishment of a causal relationship between clinical outcome and treatment, and the outcome data are probably additionally compromised by the varying durations of patient follow-up. However, as a longitudinal patient cohort study following a large, well-defined group of patients from a recognisable geographic location presenting with a specific oral disorder and undergoing a consistent treatment intervention coordinated by one clinician throughout nearly 20 years, it provides one of the most important oral potentially malignant disorder data sets yet studied in contemporary literature.

In relation to patient profiling, no specific attempts were made in this study to detail patients' general medical status or individual use of long-term pharmacotherapy. Whilst this might have provided an additional stratification of patient risk, previous work has not found these data to be especially useful in profiling PMD patients or in predicting the risk of oral carcinogenesis (Hamadah & Thomson 2009, Macfarlane et al 2012, Diajil et al 2013).

Whilst a patient cohort study of this nature is particularly suited to the analysis of a relatively rare condition such as oral potentially malignancy, reliance on pre-existing clinical records can also become a significant limitation, as detail and accuracy inevitably vary over time. It was especially disappointing, for example, to find incomplete data recorded in case notes for long-term tobacco and alcohol use during the patient follow-up period as these may be significant confounding factors influencing clinical outcome. It has, however, previously been noted that significant change or longer-term improvement in tobacco and alcohol use in Newcastle PMD patients is disappointingly poor (Hamadah et al 2007, Goodson et al 2010a).

It is probably not surprising that retrospective data should prove vulnerable to loss and contamination during 19 years of clinical study; Warnakulasuriya et al (2011) noted similar omissions in data recording when reviewing patients attending Oral Medicine clinics at Guy's Hospital in London. Fortunately, detailed tobacco and alcohol habits have been recorded in a number of previous Newcastle potentially malignant disorder studies which confirm, unsurprisingly, an important aetiological role in the local population. Thomson & Wylie (2002) first noted that, in a 57 PMD patient cohort, 79% of patients were smokers and 82% regularly consumed alcohol. In a study of a further 78 cases, Hamadah & Thomson (2009) observed that 90% were either current or ex-smokers and 78% regularly consumed greater than 30 units of alcohol per week, whilst Goodson et al (2010a) analysed another 54 patient population all of whom smoked and drank alcohol. In a further study of 96 Newcastle patients, Hamadah et al (2010) confirmed that 75% both smoked and drank alcohol regularly. Diajil et al (2013), in a 100 Newcastle PMD patient cohort study confirmed that 86% were current or ex-smokers and 83% regularly consumed alcohol.

Whilst initial clinical records in this study usually contained accurate details of patients' smoking and alcohol use, these data were not always up-dated during follow-up visits. It would not have been appropriate, therefore, to include such incomplete data in a clinical outcome analysis. It is interesting to note, however, that Hamadah & Thomson (2009) observed a trend for male patients to smoke most heavily and for smokers to be at increased risk of PMD lesion recurrence. Similarly, Goodson et al (2010a) noted an increased risk for PMD same-site recurrence in patients consuming more than 28 units per week.

In a study following PMD patients post-laser for a mean period of around 5 years, Diajil et al (2013) observed that the incidence of further PMD disease was statistically higher in patients continually exposed to tobacco, although no significant relationships between either the numbers of cigarettes smoked or the units of alcohol consumed and documented clinical outcome data were seen.

The significance of tobacco use in an oral potentially malignant disease population was, however, specifically emphasised by the findings of the Hamadah et al (2007) study, which reported upon 5-year follow-up data for 27 smokers who underwent laser excision of oral PMD lesions, and revealed that 75% still continued to smoke, despite the percentage of smokers temporarily falling to 62% at around 3-years follow-up, probably due to the temporary benefit of structured intensive, smoking cessation interventions provided during their clinic follow-up (Hamadah et al 2007).

Although patients' views and experiences regarding their PMD diagnosis and management were discussed in chapter 2, patient satisfaction and quality of life issues were not formally assessed in this clinico-pathological review. These specific areas of clinical research, however, are of particular importance in modern healthcare provision, and should certainly form an integral part of any future study.

5.6 Conclusions

Upon deciding upon an optimal management strategy for a patient with an oral potentially malignant disorder, the responsible clinician must attempt to determine the risk of cancer development in that individual, the most suitable treatment intervention and an appropriate follow-up regime to mitigate such risk (Field et al 2015). As previously discussed in this thesis, none of these aims are easily achievable, nor are they at all predictable during individual patient care.

The 590 patients reported upon and analysed in this study, however, have provided a unique insight into the natural history of PMD disease in North-East England over a 19 year period, albeit in a defined hospital population, and have also facilitated analysis of detailed clinical outcome data following a structured treatment intervention using CO_2 laser surgery. This treatment modality has proved particularly effective as a diagnostic tool, not only to provide definitive assessment of excision biopsy specimens but also to identify early cancer change. The latter finding, which occurred in 12% of this study cohort, is probably enough to justify this treatment intervention by itself. Overall, laser surgery as a treatment modality has also proved effective in removing dysplastic mucosal lesions and rendering patients free from PMD disease in nearly three quarters of the study cases.

It remains to be seen, of course, just how far these results can be extrapolated to either national or, perhaps even more pertinently, international studies, although there would appear to be consistency in the results of this MD study cohort when compared with both previous Newcastle and other clinical studies in the literature.

Chapter Six

GENERAL DISCUSSION

6.1 The Potentially Malignant State

There is little doubt, as discussed in Publication 2.5b of this thesis, that a clinically detectable disease process that is neither entirely benign nor frankly malignant remains a particularly difficult concept both for clinicians and patients alike. The specific relevance of this to overall patient management was examined in Publications 2.3a, 2.3b and 2.3c.

Potentially malignant disease presents clinically as localized 'precancerous' lesions which are non-invasive at initial diagnosis but which, through time, may transform into cancer or alternatively can regress and disappear. Any individual potentially malignant lesion may, of course, contain a range of cells with varying malignant potential (Scully & Petti 2010). Epithelial tissue throughout the upper aero-digestive tract, as well as skin, gastro-intestinal mucosa and uterine cervix, have all been identified as commonly affected sites. Uncertainty pervades all aspects of diagnosis, individual patient prognoses and interventional management techniques.

Oral potentially malignant disorders have been recognised for many years of course and a substantive literature exists, although much of it is confusing and contradictory in nature and terminology (Thomson 2012a). Rationalizing the diagnosis and management of potentially malignant disease not only offers relief from uncertainty and unpredictability but may also improve patient morbidity and reduce mortality rates from invasive cancer.

Recent attempts have been made to establish guidelines for 'pre-cancer' management, but these remain highly anecdotal and are still often based upon individual clinicians' experience and belief (Cosway & Paleri 2015, Diz et al 2015, Field et al 2015). In general, whilst treatment has been recommended to relieve symptoms and prevent malignant transformation, in Newcastle we have consistently found that interventional laser surgery also offers clarity in histopathological diagnoses alongside, perhaps most significantly, treatment efficacy and reliability (Thomson 2014). It has been the specific purpose of this thesis to examine evidence accrued from clinical studies carried out in recent years in North-East England and to thereby

challenge the, oft perceived but rarely tested, null hypothesis that treatment intervention fails to influence the progress of potentially malignant disease.

6.2 Incidence and Prevalence of Oral Potentially Malignant Disease

Reliable incidence and prevalence data for potentially malignant oral lesions remain sparse, although Napier & Speight (2008) reported a worldwide prevalence of 1 to 5% whilst Carnelio et al (2011) noted occurrence in approximately 2.5% of the general population. Diz et al (2015) quoted rates of 1 to 2% for leukoplakia, but only 0.02 to 0.83% for erythroplakia. The reality is, of course, that such figures vary by geographic region, the nature of the patient population studied and the varying disease definitions employed (Tadakamadla et al 2015). Villa & Gohel (2014) screened 3,142 patients in an USA dental hospital setting and identified 27 cases (0.9%) with an oral potentially malignant lesion, although only 3 actually exhibited dysplasia on histopathological examination. The data presented in Chapters 3, 4 and 5 in this thesis provide a unique and consistent profile of oral potentially malignant disorder patients in North-East England. Neither study, unfortunately, allows accurate incidence or prevalence calculations.

Whilst oral cancer incidence is known to be high in North-East England, it remains unclear how many invasive cancers develop from previously identifiable precursor lesions although it is not unreasonable to speculate that the majority probably do. In Publication 2.4, we discussed the difficulties inherent in trying to characterise transformation of oral precursor lesions within a specified population. A wider and particularly difficult patient management issue remains, however, which is how to identify and then target more patients with potentially malignant disease before transformation occurs to invasive cancer.

The reality is that most potentially malignant oral lesions are asymptomatic and are usually identified by dental practitioners during routine oral examinations. Unfortunately, many patients at risk of oral cancer are not regular dental attenders, and it has been observed that up to 30% of patients

with suspicious oral symptoms may also delay seeking healthcare advice for 3 months or more (Scott et al 2009).

General population screening for oral cancer is not currently supported in the UK, due to a poor evidence base, lack of specific and reliable screening tests and, perhaps of most significance, a failure to demonstrate significant improvement in overall cancer survival rates following early detection of disease (Brocklehurst et al 2013, Solutions for Public Health 2015, Warnakulasuriya et al 2015).

We have previously emphasized the pragmatic value of case finding and opportunistic testing of 'high-risk' groups to aid oral potentially malignant disorder diagnosis and facilitate interventional treatment, but these remain primarily secondary and tertiary preventive techniques which rely almost entirely upon individual patient recognition and presentation for appropriate specialist care and advice (Thomson 2012a).

In relation to PMD diagnosis, it is probably true that a thorough and methodical visual examination of the oral mucosa by an experienced clinician, supplemented by targeted incisional biopsy for provisional histopathological examination, remains the 'gold standard' assessment. Despite intensive investigation, few of the proposed adjunctive diagnostic techniques including light-based or optical inspection systems, vital tissue staining, or brush biopsy and exfoliative cytology have shown any significant benefit in contemporary clinical practice (Lingen et al 2008, Awan et al 2011a, 2011b & 2012, Thomson & Goodson 2012b, Messadi 2013, Goodson et al 2014a & 2014b, Macey et al 2015).

6.3 Early Detection of Oral Malignancy

Despite limited evidence regarding improved cancer survival rates, early diagnosis of oral malignancy must, intuitively at least, be a priority public health objective and is probably the most important single factor that improves individual patient prognosis, with cure rates approaching 90% for Stage 1 disease (Bagan et al 2010b, Leston & Dios 2010). The problem

remains, however, that most oral cancer cases are in an advanced stage at the time of clinical detection due to diagnostic delays (Gomez et al 2010, Warnakulasuriya 2010). Although targeted screening of 'high-risk' patients may be an effective strategy, Ford & Farah (2013) comprehensively reviewed a number of factors that adversely influence the early diagnosis of oral cancer and potentially malignant disease. Of particular interest was their emphasis on potential delays during the initial recognition and subsequent diagnosis of potentially malignant disease, both by patients themselves and by their primary health care practitioners. Scott et al (2009) examined perceived 'barriers' preventing patients from seeking advice on potentially malignant oral symptoms, which were often related to pre-existing health beliefs, behaviours and personal circumstances, whilst effective 'triggers' to seek help included the severity of individual patients' symptoms and the ease of access to appropriate health care services. Some of these issues were introduced in this thesis in Publication 2.3a.

Both Ford & Farah (2013) and Brocklehurst et al (2009a & 2009b) have commented upon the fundamentally important role that primary care dental practitioners may have in PMD diagnosis, but emphasized the difficulties inherent in recognising salient but subtle mucosal changes, the wide range of potentially malignant lesion presentation, problems created by a lack of systematic and rigorous oral examination techniques and underlying diagnostic uncertainties. They both recommended improvements in training and enhanced oral mucosal examination competency for general dental practitioners together with wider efforts to raise public awareness of oral malignant disease; these observations were supported by Epstein et al (2007).

Interestingly, Ford & Farah (2013) also highlighted a requirement to explore the varying needs and experiences of PMD patients during all aspects of their diagnosis, risk behaviour modification, treatment and clinic review; these observations strongly support the concepts introduced in this thesis in Publications 2.3a, 2.3b and 2.3c.

Recognising the limitations of oral cancer screening programmes, Amarasinghe et al (2010) proposed a risk-factor model, based upon questionnaire analysis of age, socioeconomic status, and tobacco, betel-quid and alcohol habits, to improve detection of oral potentially malignant disorders in a high prevalence Sri Lankan population. Whether such an approach would be applicable to a Western population remains unproven, but appropriate weighting of smoking, alcohol and other population-specific risk factors have been discussed in Publications 2.5a and 2.5b and may well prove useful tools in future clinical practice and demographic studies.

6.4 Diagnosis and Histopathological Grading

In the absence of accurate predictive biomarkers, assessment and grading of epithelial dysplasia in tissue biopsy specimens remains fundamental to both diagnosis and decision making for treatment intervention during oral potentially malignant disorder management, and yet it is an area of practice known to be fraught with subjectivity and is lacking in both intra- and inter-observer reproducibility (Bosman 2001, Sloan 2012). It has also been noted that dysplasia grading appears most reliable for 'high-grade' lesions exhibiting the most severe dysplasia changes, whereas 'low-grade' lesions appear to be at particular risk of poor objectivity (Speight et al 2015). Whilst the association between worsening grades of dysplasia identified in oral biopsies and an increasing risk of malignant transformation has long been recognised, Edwards (2014) raised genuine concerns about the validity of basing treatment decisions wholly upon dysplasia diagnoses obtained from localised, incision biopsies harvested at single time points during the lifetime and evolution of unstable mucosal lesions. Total reliance on incision biopsy results for definitive diagnoses of oral potentially malignant lesions has been criticised on a number of occasions previously (Holmstrup et al 2007, Scully & Petti 2010).

Indeed, the problems and unreliability inherent in attempting to categorize an essentially dynamic and continuous spectrum of epithelial tissue changes into discrete, arbitrary diagnostic categories have been explored in

Publication 2.5b. Nonetheless, dysplasia grading still offers the best opportunity for pathologists to convey to clinicians the nature of individual mucosal lesions and ultimately to assess the overall risk of malignancy (Edwards 2014). It was encouraging to see such consistently high levels of agreement between Newcastle oral pathologists' histopathological diagnoses in the studies reviewed in this thesis. Overall, it is quite clear that accurate diagnosis of oral potentially malignant disease relies fundamentally on the clarity of two-way communication between clinician and pathologist (Farah et al 2014).

An accurate pathological diagnosis is, of course, also dependent upon appropriate clinical sampling of oral lesions and, whilst incision biopsies harvested from the most suspicious or most representative parts of individual lesions may provide sufficient detail, multiple or 'field mapping' biopsies and laser excision samples are likely to provide more detailed information and overall provide better representation of the true nature of oral mucosal lesions (Thomson & Wylie 2002, Thomson & Hamadah 2007, Sloan 2012). These specific issues were examined in the patient cohort reviewed in Chapter 5.

Edwards (2014) also highlighted the important observation that not all neoplastic precursor lesions will exhibit the classic morphological features of epithelial dysplasia, especially those disorders exhibiting lichenoid features and verrucous hyperplasia; these issues have been reviewed in Publication 2.4 and discussed at length in Chapters 2 and 5.

This thesis was not prepared as a treatise on the histopathological diagnosis of epithelial dysplasia but, nonetheless, the recognition of dysplasia within oral mucosal biopsies plays a fundamental role in overall PMD management. As Bosman (2001) presciently observed, however, dysplasia classification is only likely to be improved upon by establishing a better understanding of the clinical progress and natural history of the potentially malignant state and by a fundamental improvement in our knowledge of the biological processes driving carcinogenesis.

6.5 Interventional Treatment for Oral Potentially Malignant Disorders

Management of oral potentially malignant disease has, for many years, been controversially polarised between surgical excision to remove identifiable mucosal lesions and more conservative medical or observational techniques (Carnelio et al 2011). As Mandal et al (2014) observed, whilst the definition of potential malignancy intuitively warrants some form of targeted management, rather than passive observation, the diverse range of treatment options quoted in the literature still confounds individual treatment decisions.

Carnelio et al (2011) and Kumar et al (2013) have recently reviewed a number of non-surgical PMD treatments including the use of antioxidant supplements such as carotenoids and retinoids, or chemotherapy with bleomycin, but significantly noted the lack of any evidence of efficacy, the risk of side effects, the high rates of recurrence reported following treatment cessation, and perhaps most pertinently no evidence whatsoever regarding effective prevention of malignancy. Interestingly, Lee et al (2000) previously reported a 31.4% malignant transformation rate in oral leukoplakias treated with isoretinoin and/or β-carotene, emphasizing the limitation of medical treatment. Marley et al (1996) noted that only 3 to 4% of UK Oral and Maxillofacial Surgeons would utilise chemo-preventive agents in PMD treatment and Kanatas et al (2013) recently confirmed this observation, in a questionnaire-based study, finding that only 2% of surgeons would ever consider medical treatment, thus demonstrating the contemporary redundancy of such treatment.

The confusion that still plagues the literature regarding oral potentially malignant disorder management was well summarised by van der Waal (2014) who, on the one hand opinions that local lesion recurrence is common following surgical treatment of leukoplakia and that neither intervention nor long term clinic follow-up is effective in reducing the risk of cancer development, whilst on the other hand makes the important observation that most PMD patients prefer treatment intervention, and has therefore come to

recommend surgical excision of localised, well-circumscribed oral mucosal lesions followed by long-term, specialist clinic follow-up.

The evidence-base for treatment intervention is both scanty and confused. Shiu & Chen (2003) attempted a systematic literature review to determine the effectiveness of treatment interventions for oral leukoplakia, the commonest PMD, but found such wide variation in diagnostic criteria, an extensive heterogeneity of proposed treatment methodologies and such disorganised patient compliance and follow-up data that they felt it was quite impossible to quantify their analysis in any meaningful way.

Lodi et al (2006) previously stated that, whilst many quoted treatment interventions may be effective in initially resolving individual oral leukoplakic lesions, clinical relapse, adverse effects and limited evidence regarding the effective prevention of malignant transformation limited the usefulness of currently available techniques. Wan et al (2014) observed that following successful primary therapy, local recurrence of leukoplakia and the development of new-site (or second primary) leukoplakias accounted for the majority of unfavourable events experienced by patients.

Despite these negative observations and the limitations in evidence-based guidelines, a number of recommendations have recently been made for oral potentially malignant disorder treatment. In 2011, for example, ENT-UK (British Association of Otorhinolaryngology-Head & Neck Surgery) published multidisciplinary management guidelines for head and neck cancer which included advice upon targeted biopsy and histopathological assessment of potentially malignant lesions, advice to patients to reduce tobacco and alcohol use, surgical excision when lesion size and post-operative function allow, together with long term clinic surveillance. Most authors now actively encourage intervention, and mucosal lesion excision rather than observation is recommended, together with long term follow-up by specialist clinicians (Kumar et al 2013, Thomson 2014, Dost et al 2014, Field et al 2015).

Although some workers have suggested that minimally invasive approaches to treat less severely dysplastic lesions may be appropriate (Huff et al 2010), Arnaoutakis et al (2013) strongly recommended excision and/or ablation of all head and neck mucosal pre-malignancy, emphasizing the high risk of recurrence and disease progression consequent upon observing, rather than treating, even mildly dysplastic oral lesions.

This has certainly been the treatment philosophy adopted in Newcastle since 1996. Excision of potentially malignant oral mucosal lesions, if necessary followed by repeat surgery when recurrence or further disease occurs as clearly demonstrated by the patient cohort presented in Chapter 5 of this thesis, facilitates not only a coordinated follow-up regime but also renders identification and diagnosis of progressive PMD disease straightforward and probably has significant health economic benefits by ultimately proving less expensive than carrying out multiple, repeated incision biopsies over many years of subsequent, observational follow-up; this is a point endorsed by Farah et al (2014).

In considering the wider aspects of health economics in relation to oral potentially malignant disorder management, details of treatment efficiency, cost and value for money all require attention, particularly in comparison to the extensive healthcare costs inevitably associated with oncology treatment. There are virtually no data in the literature to support or refute the concept that early, minimal intervention to attempt secondary or tertiary prevention of oral cancer in an ‘at risk’ population is cost-effective, but it is certainly not an unreasonable hypothesis.

In recent years the UK Department of Health has introduced Patient-Level Information and Costing Systems (PLICS) to determine healthcare resources consumed by individual patients by measuring the costs incurred by NHS healthcare organizations in providing particular treatments (http://webarchive.nationalarchives.gov.uk). Whilst still relatively new in concept, PLICS can be applied to the diagnosis and management pathway for both oral cancer and pre-cancer patients to contrast the associated healthcare costs.

PLICS data from the Newcastle upon Tyne Hospitals NHS Foundation Trust for a 6 month period (April-October 2015) are utilized in Table 6.1 to directly contrast averaged health economic calculations associated with the provision of diagnostic and surgical treatment services for interventional laser surgery of potentially malignant disease (averaged at around £997.90 per treated patient) and the multi-disciplinary care required for oral cancer (averaged at £5,471.58 per patient). Initial management of an established oral cancer thus costs more than 5 times the treatment of a pre-cancer lesion and, of course, there will be additional significant costs for head and neck cancer care including the requirement for adjuvant radiotherapy and/or chemotherapy treatments which are not included in these calculations.

Although limited in evidence, Tadakamadla et al's (2015) literature review also reported no significant adverse quality of life outcomes for oral potentially malignant disorder patients, when contrasted with the known sequelae of oral cancer treatment including pain, trismus, xerostomia, speech and swallowing disorders, along with loss of cognitive, social, physical and emotional functions (Rogers et al 2007).

TABLE 6.1: COMPARISON OF HEALTHCARE COSTS - INTERVENTIONAL CO_2 LASER SURGERY FOR ORAL PRE-CANCER VS MULTI-DISCIPLINARY CARE FOR ORAL CANCER CASES*

CO2 Laser Surgery for Oral Precancer Lesions	Cost	Income	Margin
Oral Surgery Out-Patient Appointment:			
WF01B-Non-Admitted Face To Face Attendance, First	£816,889	£1,605,630	£788,741
Activity	7,899		
Average cost and income per attendance	**£103.42**	**£203.27**	**£99.85**
Out-Patient LA Biopsy Appointment (see Oral OPROC tab):	£56,130	£137,659	£81,529
Activity	486		
Average cost and income per case	**£115.49**	**£283.25**	**£167.76**
Day Case Laser Surgery RVI Theatre (Claremont) - see Oral DC tab:	£30,381	£23,577	-£6,803
Activity	39		
Average cost and income per case	**£778.99**	**£604.55**	**-£174.44**
Total Average Oral Surgery Cost & Income	**£997.90**	**£1,091.06**	**£93.17**

Major Head & Neck Surgery (Freeman ENT)	Cost	Income	Margin
Multi-Disciplinary Clinic Attendance:			
WF02B-Multiprofessional Non-Admitted Face To Face Attendance, First	£5,859	£6,621	£762
Activity	47	47	47
Average cost and income per attendance	**£124.67**	**£140.87**	**£16.20**
Inpatient Surgery (see ENT EL detail tab):			
In-Patient Stay (Ward 10 Freeman) for approx. 14 days	£52,368		
Major Theatre (All-Day List Freeman)	£87,838		
ITU / HDU Stay (approx. 1 day)	£13,912		
All other costs	£33,024		
Total Inpatient Cost	**£187,142**	**£105,251**	**-£81,890**
Activity	35	35	35
Average cost and income per case	**£5,346.91**	**£3,007.18**	**-£2,339.73**
Total Average ENT Cost & Income	**£5,471.58**	**£3,148.05**	**-£2,323.52**
Total Length of stay for IP activity	204		
Ward cost per bed day	£256.70		

**Data Source PLICS 2015 (April – October)*

Provided by Mr. Patrick Pearce, Directorate Finance Manager, Newcastle upon Tyne Hospitals NHS Foundation Trust (January 2016)

It is also instructive to compare and contrast the potential efficacy of different PMD treatment modalities against the overall management goals initially listed in Chapter 1 of this thesis, and these are summarized in Table 6.2. This exercise again supports the assertion that surgical excision of identified oral potentially malignant lesions comes closest to being the optimal interventional management technique (Thomson 2012d).

TABLE 6.2: EFFECTIVENESS OF PMD TREATMENT MODALITIES IN ACHIEVING MANAGEMENT GOALS

		Treatment Modality	
Management Goals	**Clinical Observation**	**Medical Treatment**	**Surgical Excision**
Accurate Diagnosis	No	No	*Yes*
Early Recognition of Malignancy	Possibly	No	*Yes*
Removal of Dysplastic Mucosa	No	No	*Yes*
Prevention of Recurrent or Further PMD disease	No	No	Possibly
Prevention of Malignant Transformation	No	No	Possibly
Minimal Patient Morbidity	*Yes*	No	*Yes*

There appears, therefore, to be substantive evidence supporting diagnostic and treatment efficacy, acceptable quality of life outcomes and significant cost-effectiveness for the use of interventional laser surgery in the management of oral potentially malignant disorders.

6.6 Clinical Outcome

Uniform use of appropriate diagnostic criteria, and agreed terminology to accurately document clinical outcome data are recognised as essential for both patient management and conducting and communicating research findings (Napier & Speight 2008). It was only by undertaking long-term follow-up of a large number of PMD patients during the study reported in Chapter 5, that it was possible to recognise and then specifically define 4 important clinical outcomes:

1. Disease free patients who, following treatment intervention, no longer have identifiable oral mucosal lesions or exhibit clinical signs of PMD disease,
2. Patients with further (new-site) or persistent (same-site) PMD disease, but who ultimately achieve disease free status following additional treatment intervention(s),
3. Further (new-site) or persistent (same-site) PMD disease where clinical lesions persist following treatment, and
4. Malignant transformation, including both same-site transformation following treatment of a precursor lesion and new-site cancer development.

Each of these distinct patient groups possess important characteristics that define both their presentation and ultimate clinical course, and these have been described and analysed in detail in Chapter 5 of this thesis. In Table 6.3, consistently identified clinico-pathological features in this thesis associated with, or in some cases significantly predictive of, the varying clinical outcome categories are summarised. Where no reliable association was found, no entry is recorded against that category. Undoubtedly, careful attention to these outcome categories will be of paramount importance in future clinical studies.

TABLE 6.3: CONSISTENT CLINICO-PATHOLOGICAL FEATURES ASSOCIATED WITH DEFINED CLINICAL OUTCOME CATEGORIES

	Disease Free	**Further/Disease Free**	**Further/Persistent Disease**	**Malignant Transformation**
Patient Age	Younger*	Younger	Older	-
Clinical Lesion	Leukoplakia*	Leukoplakia	Leukoplakia	Erythroleukoplakia*
Site	-	-	Gingiva Alveolus Labial	Floor of Mouth Lateral Tongue
Treatment	-	-	Ablation*	-
Histopathology	Mild Dysplasia* No LI*	Mild / Moderate Dysplasia LI	PVL LI	Severe Dysplasia* Carcinoma in Situ* LI*
Further Disease	-	New Site	Same Site	Same Site

LI: Lichenoid Inflammation; PVL: Proliferative Verrucous Leukoplakia

**Statistical Significance*

Whilst it is indeed encouraging for the treatment intervention adopted by this author in Newcastle that over 70% of treated patients fall in to the disease free category, it is almost certainly the further and persistent PMD disease categories and the malignant transformation patient groups that represent the most aggressive potentially malignant disorders. From the data analysed in Chapter 5 of this thesis, it is possible to define an erythroleukoplakic lesion appearance and the presence of severe dysplasia or carcinoma-in-situ and lichenoid inflammatory change on histopathology examination as significant predictors of progressive PMD disease and, perhaps most importantly, of malignant transformation risk. Further, detailed clinico-pathological analyses of these patients should ultimately provide vital data to learn more about the natural history of the potentially malignant state, and these studies are now on-going in Newcastle.

Of particular importance in the future will be our ability to stratify individual patient risk (as discussed in detail in Publication 2.5b), and the differentiation of PMD cases that exhibit ‘high-risk’ disease from those at ‘low-risk’ will be a

fundamental requirement if we are to truly improve and rationalize potentially malignant disease management.

6.7 Malignant Transformation

Transformation of a pre-existing potentially malignant lesion into a frankly invasive tumour must rank as the ultimate treatment failure for PMD patients, and yet prediction of such 'high-risk' behaviour and cancer development remains elusive in clinical practice. Field et al (2015) recently quoted transformation rates for oral epithelial dysplastic lesions ranging from 6.6 to 36.4%, and 'average' transformation times varying widely between 0.5 and 17 years.

Shiu et al (2000) reported that the likelihood of malignant transformation within previously identified oral leukoplakic lesions will increase with the duration of patient follow-up, quoting a 14% rate over 10 years in a Taiwanese population. This was similar to Cowan et al (2001) who observed a 15% transformation rate in 165 oral epithelial dysplasia cases in a population from Northern Ireland. In contrast, Schepman et al (1998), Hsue et al (2007), and Warnakulasuriya et al (2011) all noted similar transformation rates of 2.9%, 3%, and 2.6% respectively in the Netherlands, Taiwan, and South-East England, although it is unclear how many initial lesions in these studies were truly dysplastic. Saito et al (2001) reported a 6.3% transformation rate in 142 patients treated by surgery for oral leukoplakia, although only 91 lesions exhibited dysplasia on initial biopsy.

Speight (2007) emphasised the importance of dysplasia severity as an indicator of transformation risk, quoting rates of 16% for severe dysplasia, between 3 and 15% for moderate dysplasia and less than 5% for mild dysplasia, but with little evidence of consistency in different studies and overall transformation rates were quoted which varied from approximately 7 to 50%. Warnakulasuriya et al (2011) also reported a significantly higher risk of cancer development with higher grades of dysplasia and a trend for that risk to increase with worsening grades of dysplasia.

It is interesting that Ho et al (2013) reported quite a high, 25%, malignant transformation rate, with a median time to transformation of 40.3 months, in 91 PMD patients formally monitored in a specialist clinic in North-West England, although no details were provided regarding PMD treatment intervention. Warnakulasuriya & Ariyawardana (2015) recently reviewed 24 observational studies of oral leukoplakia and again confirmed a wide range of malignant transformation rates varying between 0.13% and 34.0% (with a mean of 3.5%); advanced age, female patients, lesions greater than 200mm^2, non-homogenous clinical appearance and higher grades of dysplasia all appeared to increase the risk of cancer development, which are findings consistent with previously published studies (Thomson 2012e).

The patient data set presented in Chapter 5, which comprised lesions primarily exhibiting quite significant dysplasia and all treated by CO_2 laser, showed a relatively low malignant transformation rate of 4.8% during the study follow-up period; this is similar to a rate of 4.7% recently quoted by Dost et al (2014) for an Australian study population, but this was a less well-defined patient group. The much more common finding in this MD study (affecting 71 patients or 12%) was the identification and complete excision of unexpected foci of invasive carcinoma upon initial PMD lesion excision. This, of course, is actually an important diagnostic and treatment success for such an interventional treatment regime and in this context can hardly be considered as a 'treatment failure'.

Distinction should also probably be made between *malignant transformation*, which is the change of a previously identified oral precursor lesion into an invasive carcinoma at the same site, and *cancer development* which occurs when patients with pre-existing or previously treated pre-cancer lesions subsequently develop carcinoma at new, distinct intra-oral sites (Thomson 2012e). Interventional treatment to excise potentially neoplastic cells may thus help prevent malignant transformation at the site of the excised lesion but, as a consequence of field change, cancer development at new sites remains a risk. However, by ensuring that active patient surveillance and long term follow-up remain mandatory components of interventional therapy,

early signs of cancer development can be recognised and further active surgical intervention is facilitated (Thomson 2012e).

6.8 Patient Follow-Up

It is undoubtedly true that, particularly in relation to head and neck cancer, patient follow-up clinics have limited efficacy in identifying recurrent malignant disease or second primary tumours with patients themselves often alerting clinicians to suspicious signs and symptoms on their re-attendance (Cooney & Poulsen 1999, Thomson 2012d). No consensus exists in the literature to determine the exact nature or duration of patient follow-up for oral potentially malignant disease (Marley et al 1996 & 1998, Nankivell & Mehanna 2011), although evidence does exist which highlights the occurrence of further PMD disease 10 to 15 years after initial patient presentation (Thomson 2012d). Some workers have reported clinic strategies ranging from immediate post-treatment discharge to life-time follow-up (Epstein et al 2007), whilst Mehanna et al (2009) have suggested keeping PMD patients under surveillance for at least 20 years. Life-long follow-up examinations at 3 to 6 month intervals have been advised by other workers (van der Waal 2010, Kanatas et al 2011, Diajil et al 2013, Lian et al 2013, Wan et al 2014). Greaney et al (2014) also advised similar follow-up regimes for suspicious oral lichenoid lesions.

In Newcastle, PMD patients are reviewed 1-month following surgery and then at 3 to 6 month intervals dependent upon their individual clinical course and overall risk assessment; disease free patients with reduced risk factor behaviour are seen less frequently. Coordinated and detailed follow-up, supplemented by careful visualisation and inspection of the oral mucosa, can identify recurrent or further PMD disease at the earliest possible stage, alongside important opportunities to elicit the presence of early malignant change (Epstein et al 2007, Thomson 2012d). The overall objectives of a structured patient follow-up regime following potentially malignant lesion surgery may be summarized, as shown in Table 6.4.

TABLE 6.4: OBJECTIVES OF PMD PATIENT FOLLOW-UP AND SURVEILLANCE FOLLOWING TREATMENT INTERVENTION

Assess efficacy of treatment intervention
Recognise treatment complications
Early identification of recurrent or further PMD disease
Early identification of malignancy
Timing and coordination of further treatment interventions
Modify patient risk factor behaviour
Assess long-term patient risk

The precise clinical environment in which patients are followed-up is also important; carcinoma development is more likely to be diagnosed earlier with a reduction in morbidity and mortality when patients attend specialist oral oncology or potentially malignant disease clinics (Diajil et al 2013, Ho et al 2013, Thomson 2014), although it was noted in Publication 2.2 that few UK clinicians actually provide such a service.

We have previously emphasised that interventional management strategies should really be considered cyclical in nature, passing from active surgical excision through to surveillance but returning to surgical intervention upon diagnosis of further pre-cancer disease (Thomson 2012e). It is, therefore, both a consistent and a determined approach to patient management and applied rigorously has the ability to reduce the risk of invasive cancer development.

6.9 Clinical Impact of MD Thesis Research

The clinical impact of new knowledge, treatment innovation or improved management protocols can only truly be judged by the influence they ultimately have on the long-term outcome of a specified medical disorder. Despite the demonstration of new knowledge or an innovative clinical application, instigating change in established clinical practice is known to take time, often many years. It is of general importance, therefore, to improve access to clinical trial data and encourage better reporting of research

findings, although delays in information dissemination, reluctance of clinicians to alter long-established practice, cultural influences which favour preservation of the status quo and resource implications remain the principal detractors of change (Glasziou et al 2014).

The early diagnosis of oral cancer and the management of potentially malignant disorders are recognized as areas of contemporary clinical practice in which variability in decision making and a lack of high-quality evidence has confounded treatment initiatives. Perhaps of greater significance is the realization that, owing to the limited relevance of existing clinical trial data, systematic literature reviews and meta-analyses have repeatedly failed to answer the fundamental diagnostic and management dilemmas inherent in potentially malignant disease treatment and discussed in Chapter 1 of this thesis (Moles et al 2002, Downer et al 2004, Lodi et al 2006, Smith et al 2009, Mehanna et al 2009, Walsh et al 2013).

Lavelle & Scully (2007) usefully highlighted the formidable, multi-factorial influences and heterogeneous challenges that frustrate early identification of individuals at high risk of oral carcinogenesis. However, the clinical studies presented in this MD thesis, particularly the extensive patient cohort followed in Chapter 5 which combined a defined surgical intervention with detailed patient profiling and active clinic surveillance, strongly suggest that a properly coordinated and methodical clinical management protocol may have the potential to intervene to stall or even halt the inevitable process of oral carcinogenesis, although this remains unproven. Whilst efficacious for all patient groups, interventional treatment appears to be of especial relevance for those exhibiting progressive PMD disease or deemed to be at ‘high risk’ of malignant transformation.

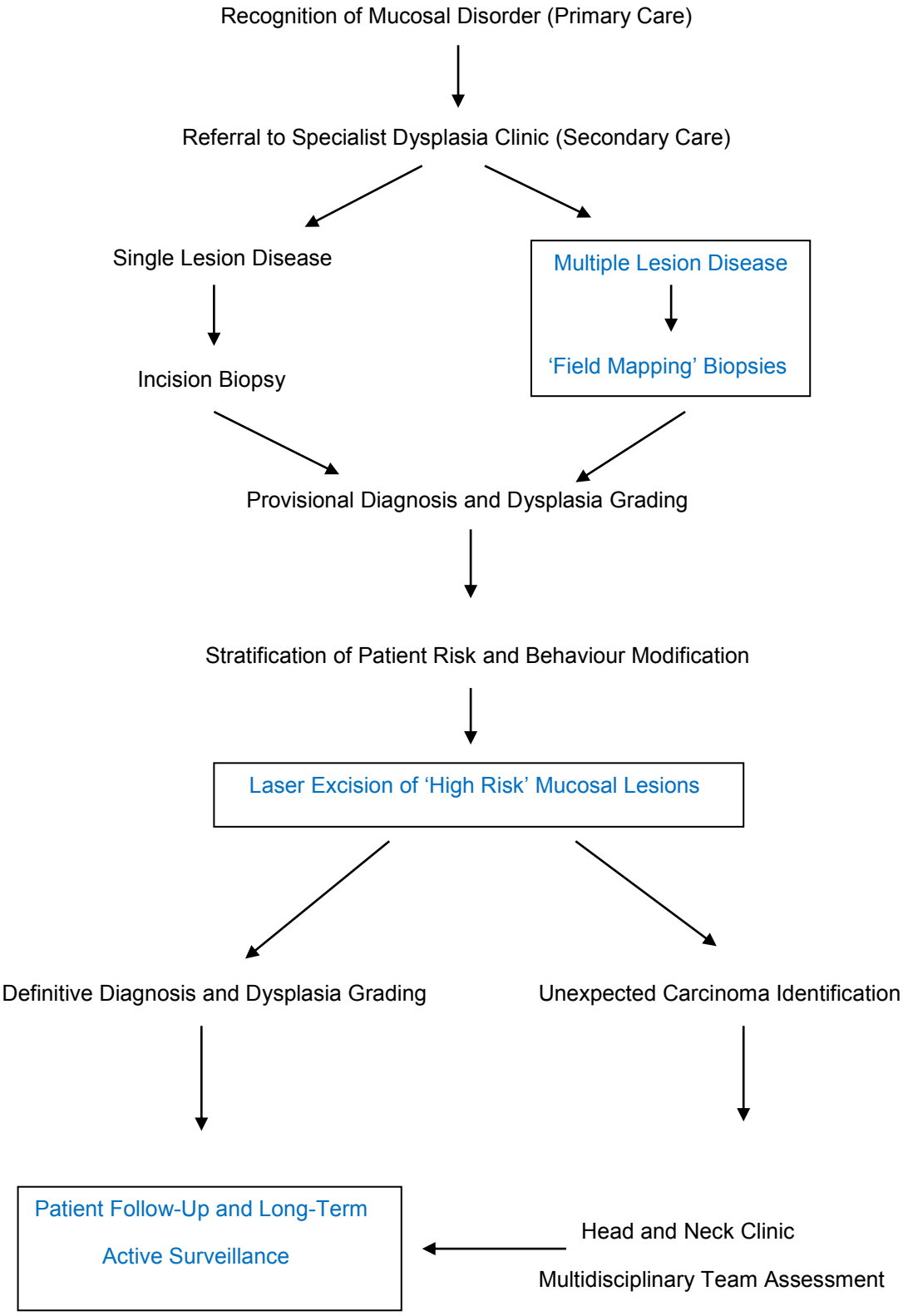
By establishing and thus defining the role of interventional laser surgery in our Newcastle clinical practice we have helped facilitate definitive oral diagnosis and efficacious low morbidity treatment (Thomson & Wylie 2002, Goodson et al 2012), reduced same-site malignant transformation rates (Thomson 2014), allowed early diagnosis and treatment of cancer (Goodson & Thomson 2011), identified patients at risk of recurrent or further PMD

disease, and helped define specific, distinct clinical outcome categories (Diajil et al 2013). It is probably true to say that surgical excision of potentially malignant oral lesions is now regarded as the preferred treatment modality in contemporary practice (van der Waal 2009, Gomes & Gomez 2013).

Active patient surveillance following interventional therapy has enhanced our understanding of the natural history of potentially malignant disease, helped identify and target high risk patients, encouraged recognition and modification of individual risk factor behaviours, highlighted the significance of multiple-lesion presentation and helped develop new techniques such as 'field mapping' biopsies to identify and treat the most significant sites of mucosal disease (Thomson 2002, Thomson & Hamadah 2007, Bagan & Scully 2008, Thomson 2012c).

Figure 6.1 summarizes the contemporaneous management pathway for oral potentially malignant disorders that has evolved following the pragmatic application of the research work presented in this thesis.

Figure 6.1: Newcastle Management Protocol for Oral Potentially Malignant Disorders



There are 3 fundamental areas of clinical practice which are significantly influenced by the research studies presented in this thesis:

1. Perhaps of greatest importance is the widespread acknowledgement that observational or medical treatments are ultimately unsatisfactory in potentially malignant disorder management (Dionne et al 2014), and that formal surgical excision of oral mucosal lesions is necessary for both definitive diagnosis of the presenting condition and an ultimately successful treatment intervention (Thomson & Wylie 2002, Mehanna et al 2009, van der Waal 2010, Balasundaram et al 2013, Thomson 2012c, Thomson 2014).

2. There is now increased realization that field cancerization effects within the oral cavity may be much more significant than previously recognized and that multiple lesion disease may well represent a distinct disease entity with an increased risk of malignancy requiring proactive, targeted treatment intervention (Thomson 2002, Thomson & Hamadah 2007, Hamadah et al 2010, Arduino et al 2013, Kumar et al 2013, Wan et al 2014).

3. Recognition that patient profiling, risk factor stratification and active long-term surveillance are all part of the fundamental management strategy for patients, which commences at the point of PMD diagnosis and continues during interventional treatment and throughout long-term follow-up. The specific role of dedicated specialist clinics has also evolved through recognition of the significant practical benefits they bring to both patients and clinicians (Kanatas et al 2011, Thomson 2012c, Ho et al 2013).

6.10 Limitations of MD Research Work and Suggestions for the Future

As a one-centre, UK-based, clinical academic unit, there are clearly limitations to the significance and applicability of Newcastle's oral potentially malignant disease research work on a worldwide basis. However, the breadth of work reported in this MD thesis and, in particular, the unique long-term nature of the clinical study reported in Chapter 5, its large sample size of 590 well-defined cases and the methodical and coordinated treatment intervention applied to the patient cohort, provides one of the most important and detailed PMD clinico-pathological databases yet reported in the literature, and it is clear that overall this programme of research has informed and helped influence contemporary clinical practice over recent years.

Research priorities for the future were usefully summarised by Mehanna et al (2009) and included: developing effective prognostic or predictive markers in clinical practice, rationalising patient follow-up regimes, determining the efficacy of post-treatment surveillance in the early detection of PMD recurrence and malignant transformation, and refining less invasive but effective treatment interventions. Much of the work presented in this MD thesis concurs, and has attempted to contribute to the development of such a programme.

Holmstrup (2009) and Smith et al (2009) both emphasized the importance of uncertainty which still pervades all aspects of pre-cancer treatment, and also stated that it was undoubtedly time to develop a definitive and relevant prospective, multi-centre trial with long term patient follow-up and appropriate bio-molecular analyses to enhance oral cancer diagnostic science and define the role of interventional management in PMD treatment in the 21st Century.

A well-designed, randomized trial is thus now essential to provide the best evidence of effectiveness of surgical intervention in oral potentially malignant disease. To succeed and provide meaningful results, however, the trial must be based upon a firm understanding of the scientific basis of oral carcinogenesis, an enhanced knowledge of the natural history of the potentially malignant state and ensure that effective treatment modalities are utilized with full and appropriate clinician engagement. Particular difficulties

exist in establishing surgeons' equipoise and in challenging long-established practices and beliefs (McCulloch et al 2002, Potter et al 2014). Core clinical outcomes, such as disease activity, treatment efficacy, quality of life and health resource utilization, must be defined and relevant clinician and patient viewpoints incorporated into study protocols (Harman et al 2013). Feasibility and internal pilot studies are likely to be required to ensure trial validity. Much of this preliminary work has now begun, however, and is discussed in publications 2.3 and 2.5b, and by Ford & Farah (2013), Green (2013), Thomson (2014) and Tadakamadla et al (2015).

PMD trials have ultimately proved unsuccessful in the past because of fundamental flaws in patient recruitment, ill-defined disease stratification, lack of clinician agreement and ineffective treatment intervention. Nankivell et al (2012), for example, recently documented insurmountable difficulties in attempting to run a UK-based oral dysplasia trial which resulted in early study closure due to patient recruitment failures. The clinician involvement project reported in Publication 2.2 should help address many of these potential problems in designing a relevant and pragmatic clinical trial for the future, although it is recognised there are many practical difficulties to overcome especially in attempting to randomize treatment interventions and develop ethically and clinically acceptable patient control groups.

It is thus hoped that the academic work presented in this MD thesis has not only facilitated the implementation of a rational and pragmatic approach to the early diagnosis of oral malignancy, the stratification of cancer risk and the management of potentially malignant disease, but will also contribute to a demonstrable and pragmatic 'launch-pad' to facilitate the design, conduct and analysis of the long overdue definitive, randomized clinical trial for oral potentially malignant disorder management.

6.11 Treatment Recommendations

In terms of contemporaneous PMD patient management, there seems little benefit in supporting a policy of observation or 'watch and wait'; the consequences for an individual patient of developing an invasive oral squamous carcinoma within the oral cavity can be devastating and life-threatening (Thomson 2014). Interventional laser surgery, on the other hand, is recommended as a definitive treatment modality for effective removal of mucosal PMD disease, definitive histopathological diagnosis and early interventional treatment for occult malignancy. There is, however, as discussed previously an urgent need to establish multi-centre, randomized controlled trials to confirm the overall efficacy of such treatment.

6.12 Future Considerations Regarding Oral Potentially Malignant Disorder Diagnosis and Management

It is probably accurate to state that attempts to establish the true carcinogenic risk for oral potentially malignant lesions will be the subject of epidemiological, diagnostic, histopathological, bio-molecular and translational clinical research for many years to come. The precise interplay of these factors is a complex process, however, and malignant transformation is most likely to result from a combination of intrinsic and extrinsic influences acting both synchronously and metachronously in any individual patient. Only by gaining better understanding of the mechanisms involved in oral carcinogenesis will we be able to improve prevention, early diagnosis, treatment and prognosis for both oral pre-cancer and ultimately invasive squamous cell carcinoma itself (Thomson & Goodson 2012c).

In the future, with the rates of new oral cancer cases rising, it will become increasingly important to strengthen efforts to facilitate primary prevention of oral potentially malignant disease, particularly in raising wider public health awareness. There is clear evidence that cessation of smoking may result not only in the clinical resolution of established potentially malignant lesions but also help prevent further disease following treatment. Thus, greater and improved emphasis on smoking cessation initiatives remains highly pertinent

in modern clinical practice and this, together with recognition and attention to excessive alcohol consumption and improved diet, are probably most effective if provided directly to patients as part of specialist potentially malignant disorder services (Hamadah et al 2007, Goodson et al 2010).

In publication 2.2, following widespread clinicians' opinion canvassing, it is clear that there is poor coordination of potentially malignant disorder services in the UK and this author is convinced that centralisation of PMD patients in dedicated clinics with consistent, continually reinforced specialist advice and treatment together with multidisciplinary support particularly for identifying and modifying risk factor behaviours provides the optimum management strategy. In the future, it would be more sensible for dedicated PMD clinics to be established to concentrate clinical experience, facilitate rigorous audit, research and encourage new treatment trials rather than current arrangement whereby patients attend a variety of different surgical or medical clinics dependent primarily upon local or historical clinic arrangements (Thomson 2012c, 2014).

The relevance of risk in relation to potentially malignant disease has been explored in Publications 2.5a and 2.5b. We have tried in our clinics to delineate PMD patients thought to be at 'high-risk' from those deemed 'low-risk'. Based upon a combination of their age, sex, medical background and risk factors, together with the anatomical site, size, clinical appearance and histopathology of their presenting oral lesions, this is designed to identify those cases requiring urgent or more systemic interventional treatment to try to prevent cancer development. Clinico-pathological features most associated with, or indeed predictive of, specific post-treatment clinical outcomes were listed in Table 6.3.

We believe this is an appropriate and pragmatic approach to current patient management, but it remains a somewhat crude decision making tool. Recent research, after an inauspicious beginning, has again started to focus on alterations in DNA content (aneuploidy) within oral mucosal lesions as a potential marker of aggressive behaviour and increased cancer risk, although there are as yet no clinically relevant diagnostic tests available (Torres-

Rendon et al 2009, Gouvea et al 2013). Sperandio et al (2013), in a retrospective analysis of 273 oral dysplasia cases, observed a higher predictive value for malignant transformation by combining DNA ploidy analysis with dysplasia grading and also suggested that ploidy analysis might be able to detect additional 'at risk' lesions in the absence of dysplasia.

In the future, PMD treatments should ideally become much more individualised and patient specific based upon molecular profiling and targeted therapeutic intervention. Molecular targeted therapy, for example, may inhibit tumour growth and metastasis by targeting the tumour microenvironment or vasculature, or specifically focussing on protein and signal transduction pathways in neoplastic tissue leaving normal cells unaffected (Thomson & Goodson 2012c).

Central to future developments in oral oncology is the need to improve knowledge and understanding of molecular biology. As our ability to identify molecular alterations associated with various disease states increases, the requirement to analyse these for diagnostic and therapeutic purposes grows. Unfortunately, contemporary bio-molecular analyses do not provide practical or reliable diagnostic or predictive tools for the clinical management of oral oncology patients (The Cancer Genome Atlas Network 2015). Similarly, there are no markers that reliably predict malignant transformation in an individual patient with an oral potentially malignant lesion (Smith et al 2009, van der Waal 2010).

The ultimate aim of genotype based predictive tests must be, of course, the ability to stratify risk, determine prognosis and thus personalise therapeutic intervention at an individual patient level (Ye et al 2008, Hingorani et al 2010).

Clinical outcomes following oral malignancy treatment will only improve by earlier detection of cancer and effective management of precursor lesions with malignant potential (Mishra 2012). daSilva et al (2011) believe that advances in oral cancer biology offer unprecedented opportunities for future translational research with clinical impact. It is important to remember, however, that many putative markers of carcinogenesis require validation

before clinical use and that, as Mishra (2012) observed, others will only be relevant to patients from specific geographical locations and will vary with race, lifestyle and both type and amount of carcinogen exposure.

In the future we will need to definitively classify PMD patients into ‘high’ and ‘low risk’ categories and delineate individually tailored treatment protocols based upon bio-molecular profiling to target the salient markers of dysplastic change, to facilitate genetic profiling of abnormal mucosa, and to quantify the risk of malignant transformation and predict outcome.

A variety of treatment strategies, ideally marshalling systemic therapies, will be required for patients in differing risk categories. Better clinical outcomes will require improved response rates to interventional treatment and, perhaps, an enhanced immune response to fundamentally challenge the ‘premalignant’ state (Thomson & Goodson 2012c).

Chapter Seven

GENERAL CONCLUSIONS

7.1. Introduction

Having reviewed contemporaneous and relevant literature regarding oral carcinogenesis and potentially malignant disorders in Chapter 1, and then having presented and discussed a number of recent, pertinent papers by this author relating to patient, clinician, and diagnostic PMD parameters in Chapter 2, the principal aim of this MD thesis was to undertake a comprehensive review of patient demographics and clinico-pathological data from patients presenting to a specialist, oral potentially malignant disorder service in a university teaching hospital in North-East England (Chapter 3), to determine both the appropriateness and the usefulness of treatment and the clinical outcomes following interventional laser surgery and thereby to attempt an objective assessment of the overall effectiveness of interventional PMD management (Chapters 4 and 5).

It remains problematic to definitively characterise the demographic and clinico-pathological profile of oral potentially malignant disease in the UK but the data reviewed in Chapters 3 and 4 usefully 'sets the scene' for North-East England and appears consistent over the last decade when compared with the un-published data presented in Appendix III. Unlike malignant neoplasms, however, there are no comprehensive classification systems for potentially malignant disease and, as an illustration of such difficulties globally, the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) is particularly unhelpful as a diagnostic tool including only 'leukoplakia and other disturbances of oral epithelium, including tongue' (Chapter XI; K13.2) as the only relevant PMD entry (WHO 2010).

By attempting to characterise the presentation of oral potentially malignant disease within a defined, specialist clinical service in Newcastle upon Tyne and then reviewing the clinical outcomes following a specific and coordinated treatment intervention in a longitudinal patient cohort study it was the author's intent to substantially add to the current knowledge base regarding both diagnosis and management of the oral potentially malignant state.

7.2. Response to the Study Hypotheses

In Chapter 1, a number of specific hypotheses pertinent to both the diagnosis and management of oral potentially malignant disease were highlighted for testing during the collation and analysis of the clinical and pathological study data presented in this thesis. Responses to these hypotheses will now be reviewed.

7.2.1. Assessment of standard clinico-pathological features cannot predict disease progression or clinical outcome for oral potentially malignant disorders.

Whilst this hypothesis is partially supported, clinical study results analysed in Chapter 5 have shown that certain, salient clinico-pathological features may provide pragmatic guidance regarding prognosis during the overall management of PMD patients. For example, as summarised in sections 5.4.7 through 5.4.9, increased patient age, oral mucosal lesions presenting as erythroleukoplakias, identification of severe epithelial dysplasia on histopathological examination, together with the presence of lichenoid inflammation and proliferative verrucous leukoplakia, were all associated with either progressive PMD disease or malignant transformation.

Although it is clear that further research is warranted to delineate the relevance and importance of individual clinico-pathological factors in the prediction of clinical behaviour of oral potentially malignant lesions, these specific observations are of considerable practical value during the 'day-to-day' management of individual PMD patients.

7.2.2. Incision biopsy techniques are insufficient for definitive histopathological diagnosis, which requires whole lesion excision for microscopic examination.

This hypothesis is strongly supported by the work presented in this thesis, in particular the direct comparison carried out between 609 incision and excision biopsy diagnoses obtained during the clinical study reported in

Chapter 5, and analysed in detail in section 5.4.3. Perhaps of most clinical significance were the observations that histopathological agreement was seen in only 50% of cases (307), whilst 36% (220) required 'up-grading' to more significant epithelial dysplasia or even a diagnosis of cancer following laser excision (Figure 5.3), together with the poor sensitivity of incision biopsy as a diagnostic technique to identify invasive carcinoma in oral potentially malignant lesions.

The important clinical relevance of this hypothesis is, therefore, that whole mucosal lesion excision should be considered mandatory for definitive histopathological diagnosis of oral potentially malignant lesions, and the practical realization is that such diagnosis is readily facilitated by the use of interventional CO_2 laser surgery as a treatment modality.

7.2.3. Interventional laser surgery is an effective tool for definitive diagnosis and effective treatment of potentially malignant lesions.

This hypothesis is strongly supported. Firstly, by the evidence discussed in section 7.2.2 in relation to the improved reliability of histopathological diagnoses obtained from laser excision biopsy specimens. Secondly, by the body of evidence presented in section 5.4.5 in Chapter 5 that showed that interventional surgical treatment of 590 PMD patients rendered 438 (74.2%) disease free.

The implication for clinical practice is clear. Based upon the study results of this thesis, intervention to excise identifiable potentially malignant oral lesions improves diagnostic accuracy and is effective in rendering the majority of cases disease free. Observation alone as a treatment modality, on the other hand, offers little to commend it as an appropriate management tool.

7.2.4. Active intervention during the progress of 'pre-malignancy' halts the progress of oral carcinogenesis and reduces the risk of cancer development.

This hypothesis remains unproven. Despite a body of evidence presented in Chapter 5 that showed significant diagnostic and treatment benefits resulting from the interventional surgical treatment of the 590 study patients and the successful removal of oral potentially malignant lesions achieving disease free status for 438 (74.2%), 99 (16.8%) developed invasive squamous carcinoma diagnosed either following initial laser surgical excision or by further biopsy during subsequent post-operative follow-up. Whilst 71 patients (12%) benefitted, in a clinically highly significant and fortuitous manner, from the early diagnosis and effective treatment of an unexpected carcinoma following laser excision, this cannot be considered to equate with 'halting' the carcinogenic process. Similarly, 19 patients (3.2%) out of the 28 (4.8%) who developed carcinoma during follow-up did so at new, distinct oral sites distant from their presenting lesions so that 'one-site laser surgery' will clearly not 'reduce the risk' of new-site cancer development.

Whilst a definitive clinical recommendation is difficult with this evidence base, it seems clear that a treatment intervention such as CO_2 laser surgery which reliably facilitates the early diagnosis of occult malignancy offers significant practical value as a significant preventive technique.

7.3. Additional Observations

In addition to the formal responses to the tested hypotheses, a number of additional, general observations regarding oral potentially malignancy diagnosis and management may be made following review of the clinical work presented in this thesis.

7.3.1. Potentially Malignant Disease Diagnosis. This is recognised as an on-going difficulty in contemporary clinical practice, not only in terms of accurately defining what constitutes a potentially malignant disease state but

also in managing individual presenting patients and their oral lesions. Oral potentially malignant disorders demonstrate a considerable heterogeneity in clinical presentation with an unpredictable potential for change over time and it must, therefore, be recommended that oral clinicians remain alert for signs of potentially malignant lesions together with early cancer development in all patients when performing routine oral and dental examinations. Whilst this may be especially relevant for patients who use tobacco and regularly consume alcohol, it has been clearly shown by the work of this thesis that patient risk profiling remains a complex task and that individual clinicians' experience and appropriate suspicion remain the most applicable and consistently reliable diagnostic tools. Provision of specialist PMD services, emphasizing consistency in clinical management and patient education together with coordinated post-operative follow-up regimes, offer the best opportunities for definitive diagnoses and treatment.

7.3.2. Interventional Management. Surgical excision of oral potentially malignant lesions is probably the optimal management technique facilitating definitive histopathological diagnosis, early recognition and treatment of malignancy, effective removal of dysplastic tissue, minimal patient morbidity and the likelihood of reducing the risk of further PMD disease. Continued, active surveillance for all patients post-treatment remains essential, but the frequency and duration of that follow-up is probably best 'tailored' to individual patient risk. This, hopefully, will become a pragmatic clinical tool in the years ahead, based more firmly upon individual patient genetic profiling and bio-marker analysis.

7.3.3. Clinical Outcome. The ability to predict clinical outcome for individual patients or potentially malignant lesions is still somewhat elusive in clinical practice, although a number of significant predictors of outcome have been identified in this thesis. Defining the parameters by which outcome are measured and the longitudinal study of patient cohorts offer the best opportunities to improve our understanding of the natural history of oral

potentially malignant disease, and ultimately to determine the efficacy of treatment intervention.

7.3.4. Malignant Transformation. Oral potentially malignant disorders have a variable and unpredictable risk of squamous carcinoma development. Malignant disease can arise at the site of a precursor lesion as transformation or as new site disease at distant oral sites as a result of field cancerisation. Whilst interventional laser surgery may reduce the risk of same-site transformation, and also offers opportunities to diagnose and effectively treat occult invasive carcinomas, new-site cancer development remains an unquantifiable risk for all PMD patients.

7.4. Conclusions

In a North-East England population, we have characterised that PMD patients most commonly present in the 5th and 6th decades of their life, with a distinct male predominance and an overwhelming predilection for individual mucosal lesions to arise as leukoplakias on floor of mouth and ventrolateral tongue sites, usually exhibiting features of epithelial dysplasia and increasingly proliferative verrucous leukoplakia on histopathological examination.

Overall, the recognisable clinical manifestations of potentially malignant disease present clinicians with a 'therapeutic window' of opportunity to intervene during the process of oral carcinogenesis, although in reality this window may be unpredictably opaque (Thomson 2012f). It is the author's opinion that the interventional surgical management technique presented and discussed in this thesis provides a readily available, effective and low morbidity treatment which is successful in excising or ablating PMD mucosal lesions, facilitates early diagnosis of occult malignancy, and which may help reduce the overall risk of squamous carcinoma development in individual patients particularly at the site of previously identifiable precursor lesions.

The risk of recurrent or further potentially malignant disease development and ultimately malignant transformation, however, has been shown to increase with the length of patient follow-up post-intervention. Continued, active surveillance of all PMD patients thus remains essential to ensure early recognition of such adverse outcomes which arise almost certainly as a consequence of field cancerization. Precise data governing the length of patient follow-up or the optimal time intervals between appointments are not known at present and require further research. Multi-centre, prospective, ideally randomized, controlled trials are now needed to confirm the efficacy of interventional laser surgery, to better delineate the nature of patients with progressive PMD disease, and to disseminate research findings more widely. It is hoped that the clinical work carried out over nearly 20 years by this author and presented and analysed in this MD thesis will help inform and encourage further relevant research into oral potentially malignant disease and thus ultimately lead to a reduction in the incidence of disease and an improvement in morbidity and mortality outcomes for invasive oral squamous cell carcinoma.

Chapter Eight

REFERENCES

Al Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M (2007). Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103 : e1–12.

Arnaoutakis D, Bishop J, Westra W, Califano JA (2013). Recurrence patterns and management of oral cavity premalignant lesions. *Oral Oncology* 49 : 814-817.

Amarasinghe HK, Johnson NW, Lalloo R, Kumaraarachchi M, Warnakulasuriya S (2010). Derivation and validation of a risk-factor model for detection of oral potentially malignant disorders in populations with high prevalence. *British Journal of Cancer* 103 : 303-309.

Anantharaman D, Marron M, Lagiou P, E Samoli E, Ahrens W, Pohlabeln H, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Castellsague X, Agudo A, Talamini R, Barzan L, Macfarlane T, Tickle M, Simonato L, Canova C, Conway D, McKinney P, Thomson PJ, Znaor A, Healy C, McCartan B, Hashibe M, Brennan P, Macfarlane G (2011). Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. *Oral Oncology* 47 : 725-731.

Anantharaman D, Gheit T, Waterboer T, Abedi-Ardekani B, Carreira C, McKay-Chopin S, Gaborieau V, Marron M, Lagiou P, Ahrens W, Holcatova I, Merletti F, Kjaerheim K, Talamini R, Simonato L, Castellsague X, Macfarlane T, Biggs A-M, Thakker N, Znaor A, Thomson PJ, Canova C, Conway D, Healy C, Tommasino M, Pawlita M, P Brennan P (2013). Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. *Journal of the National Cancer Institute* 105 : 536-545.

Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, Broccoletti R (2009). Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. *J Oral Pathol Med* 38 : 540-544.

Arduino PG, Bagan J, El-Naggar AK, Carrozzo M (2013). Urban legends series: oral leukoplakia. *Oral Diseases* 19 : 642-659.

Ahrens W, Pohlabeln H, Foraita R, Nelis M, Lagiou P, Lagiou A, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane TV, Macfarlane GJ, Lee Y-C, Talamini R, Barzan L, Canova C, Simonato L, Thomson PJ, McKinney PA, McMahon AD, Znaor A, Healy CM, McCartan BE, Metspalu A, Marron M, Hashibe M, Conway DI, Brennan P (2014). Oral health, dental care and mouthwash use associated with upper aerodigestive tract cancer. *Oral Oncology* 50 : 616-625.

Awan KH, Morgan PR, Warnakulasuriya S (2011a). Evaluation of an autofluorescence based imaging system (VELscope™) in the detection of oral potentially malignant disorders and benign keratosis. *Oral Oncology* 47 : 274-277.

Awan KH, Morgan PR, Warnakulasuriya S (2011b). Utility of chemiluminescence (ViziLite TM) in the detection of oral potentially malignant disorders and benign keratosis. *J Oral Pathol Med* 40 : 541-544.

Awan KH, Yang YH, Morgan PR, Warnakulasuriya S (2012). Utility of toluidine blue as a diagnostic adjunct in the detection of potentially malignant disorders of the oral cavity – a clinical and histological assessment. *Oral Diseases* 18 : 728-733.

Bagan JV, Scully C (2008). Recent advances in Oral Oncology 2007: Epidemiology, aetiopathogenesis, diagnosis and prognostication. *Oral Oncology* 44 : 103-108.

Bagan JV, Scully C, Jimenez Y, Martorelli M (2010a). Proliferative verrucous leukoplakia: a concise update. *Oral Diseases* 16 : 328-332.

Bagan JV, Sarrion G, Jimenez (2010b). Oral cancer: clinical features. *Oral Oncology* 46 : 414-417.

Bagan JV, Jimenez-Soriano Y, Diaz-Fernandez JM, Murillo-Cortes J, Sanchis-Bielsa JM, Poveda-Roda R, Bagan L (2011). Malignant transformation of proliferative verrucous leukoplakia to oral squamous cell carcinoma: a series of 55 cases. *Oral Oncology* 47 : 732-735.

Balasundaram I, Payne KFB, Al-Hadad I, Alibhai M, Thomas S, Bhandari R (2013). Is there any benefit in surgery for potentially malignant disorders of the oral cavity? *J Oral Pathol Med* 43 : 239-244.

Ball D (2008). Is the oral & maxillofacial oncology / dysplasia clinic at Newcastle General Hospital meeting the two week wait for urgent referrals? A prospective audit. *Unpublished Audit Data; Appendix 1.*

Bosman FT (2001). Dysplasia classification: pathology in disgrace? *Journal of Pathology* 194 : 143-144.

Boyle JO (2001). Retinoid mechanisms and cyclins. *Current Oncology Reports* 3 : 301-305.

Boyle JO (2004). Cyclooxygenase inhibition as a target for prevention of tobacco-related cancers. *Clinical Cancer Research* 10 : 1557-1558.

Brennan M, Migliorati CA, Lockhart PB, Wray D, Al-Hasimi I, Axell T (2007). Management of oral epithelial dysplasia: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103 (suppl 1): s19.e1-s19.e12

Brocklehurst PR, Baker SR, Speight PM (2009a). A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 1. Factors influencing detection and the decision to refer. *British Dental Journal* E3 DOI: 10.1038/sj.bdj.2010.54.

Brocklehurst PR, Baker SR, Speight PM (2009b). A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 2. Mechanics of the referral and patient communication. *British Dental Journal* E4 DOI: 10.1038/sj.bdj.2010.55

Brocklehurst PR, Kujan O, O'Malley LA, Ogden GR, Shepherd S, Glenny AM (2013). Screening programmes for the early detection and prevention of oral cancer. Cochrane Database of Systematic Reviews 11 : CD004150 DOI: 10.1002/14651858.CD004150.pub4.

Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I (2013). Treatment results of CO_2 laser vaporisation in a cohort of 35 patients with oral leukoplakia. *Oral Diseases* 19 : 212-216.

Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I (2014). Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. *Oral Diseases* 20 : e19-24.

Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W, Sidransky D (1996). Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Research* 56 : 2488-2492.

The Cancer Genome Atlas Network (2015). Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* 517 : 576-582.

Campo-Trapero J, Cano-Sanchez J, Palacios-Sanchez B, Sanchez-Gutierrez JJ, Gonzalez-Moles MA, Bascones-Martinez A (2008). Update on molecular pathology in oral cancer and precancer. *Anticancer Research* 28 : 1197-1206.

Carnelio S, Rodrigues GS, Shenoy R, Fernandes D (2011). A brief review of common oral premalignant lesions with emphasis on their management and cancer prevention. *Indian Journal of Surgery* 73 : 256-261.

Castagnola P, Malacarne D, Scaruffi P, Maffei M, Donadini A, DiNallo E, Coco S, Tonini GP, Pentenero M, Gandolfo S, Giaretti W (2011). Chromosomal aberrations and aneuploidy in oral potentially malignant lesions: distinctive features for tongue. *BMC Cancer* http://www.biomedcentral.com/1471-2407/11/445

Cerero-Lapiedra R, Balade-Martinez D, Moreno-Lopez L-A, Esparza-GomezG, Bagan JV (2010). Proliferative verrucous leukoplakia: a proposal for diagnostic criteria. *Med Oral Patol Oral Cir Bucc* 15 : e839-e845.

Chandu A, Smith ACH (2005). The use of CO_2 laser in the treatment of oral white patches: outcomes and factors affecting recurrence. *Int J Oral Maxillofac Surg* 34 : 396-400.

Chiesa F, Sala L, Costa L, Moglia D, Mauri M, Podrecca S, Andreola S, Marchesini R, Bandieramonte G, Bartoli C (1986). Excision of oral leukoplakias by CO2 laser on an out-patient basis: a useful procedure for prevention and early detection of oral carcinomas. *Tumori* 72 : 307-312.

Chiesa F, Boracchi P, Tradati N, Rossi N, Costa L, Giardini R, Marazza M, Zurrida S (1993). Risk of preneoplastic and neoplastic events in operated leukoplakias. *Eur J Cancer B Oral Oncol* 29B : 23-28.

Chuang S-C, Jenab M, Heck J, Bosetti C, Talamini R, Matsuo K, Castellsague X, Franceschi S, Herrero R, Winn D, LaVecchia C, Morgenstern H, Zhang Z-F, Levi F, Dal Maso L, Kelsey K, McClean M, Vaughan T, Lazarus P, Muscat J, Ramroth H, Chen C, Schwartz S, Eluf-Neto J, Hayes R, Purdue M, Boccia S, Cadoni G, Zaridze D, Koifman S, Curado M, Ahrens W, Benhamou S, Matos E, Lagiou P, Szeszenia-Dabrowska N, A Olshan A, Fernandez L, Menezes A, Agudo A, Dault A, Merletti F, Macfarlane GJ, Kjaerheim K, Mates D, Holcatova I, Schantz S, Yu G-P, Simonato L, Brenner H, Mueller H, Conway D, Thomson PJ, Fabianova E, Znaor A, Rudnai P, Healy CM, Ferro G, Brennan P, Boffetta P, Hashibe M (2012). Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 23 : 69-88.

Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD (2008). Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *Int J Cancer* 122 : 2811-2819.

Conway DI, McKinney PA, McMahon AD, Ahrens W, Schmeisser N, Benhamou S, Bouchardy C, Macfarlane GJ, Macfarlane TV, Lagiou P, Minaki P, Bencko V, Holcatova I, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Talamini R, Barzan L, Canova C, Simonato L, Lowry RJ, Znaor A, Healy CM, McCartan BE, Marron M, Hashibe M, Brennan P (2010). Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. *European Journal of Cancer* 46 : 588-598.

Conway DI, Brenner D, McMahon A, Macpherson L, Agudo A, Ahrens W, Bosetti C, Brenner H, Castellsague X, Chen C, Curado M, Curioni O, Dal Maso L, Daudt A, de Gois Filho J, D'Souza G, Edefonti V, Fabianova E, Fernandez L, Franceschi S, Gillison M, Hayes R, Healy CM, Herrero R, Holcatova I, Jayaprakash V, Kelsey K, Kjaerheim K, Koifman S, La Vecchia C, Lagiou P, Lazarus P, Levi F, Lissowska J, Luce D, Macfarlane TV, Mates D, Matos E, McClean M, Menezes A, Menvielle G, Merletti F, Morgenstern H, Moysich K, Muller H, Muscat J, Olshan A, Purdue M, Ramroth H, Richiardi L, Rudnai P, Schantz S, Schwartz S, Shangina O, Simonata L, Smith E, Stucker I, Sturgis E, Talamini R, Thomson PJ, Vaughan T, Wei Q, Winn D, Yu G-P, Zhang Z-F, Znaor A, Boffetta P, Ghodrat M, Lee Y, Hashibe M, Brennan P (2014). Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. *International Journal of Cancer* doi: 10.1002/ijc.29063.

Cooney RT, Poulsen MG (1999). Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? *Archives of Otolaryngology-Head & Neck Surgery* 125 : 379-382.

Cosway B, Paleri V (2015). Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *The Journal of Laryngology & Otology* 129 : 598-599.

Cowan GC, Gregg TA, Napier SS, McKenna SM, Kee F (2001). Potentially malignant oral lesions in Northern Ireland: a 20-year population-based perspective of malignant transformation. *Oral Diseases* 7 : 18-24.

Cox G, Alcock C, Corbridge R (1999). Treatment of oral cancer. Biopsy under local anaesthetic is inadequate. *British Medical Journal* 319 : 706.

Cruz I, Napier SS, van der Waal I, Snijders PJF, Walboomers JMM, Lamey PJ, Cowan CG, Gregg TA, Maxwell P, Meijer CJLM (2002). Suprabasal p53 immunoexpression is strongly associated with high grade dysplasia and risk for malignant transformation in potentially malignant oral lesions from Northern Irreland. *J Clin Pathol* 55 : 98-104.

Dakubo GD, Jakupciak JP, Birch-Machin MA, Parr RL (2007). Clinical implications and utility of field cancerization. *Cancer Cell International* doi:10.1186/1475-2867-7-2

Del Corso G, Bartolomeo Gissi D, Tarsitano A, Costabile E, Marchetti C, Montebugnoli L, Foschini MP (2015). Laser evaporation versus laser excision of oral leucoplakia: a retrospective study with long-term follow-up. *Journal of Cranio-Maxillo-Facial Surgery* 43 : 763-768.

Department of Health (2007). Cancer Reform Strategy. *London: The Department of Health.*

Deppe H, Mucke T, Hohlweg-Majert B, Hauck W, Wagenpfeil S, Holzle F (2012). Different CO_2 laser vaporization protocols for the therapy of oral precancerous lesions and precancerous conditions: a 10 year follow-up. *Lasers Med Sci* 27 : 59-63.

Diajil AR, Goodson ML, Thomson PJ (2010). Risk factors and oral precancer: developing a high/low risk profiling system. *European Archives of Otorhinolaryngology* 267 (Suppl 1) : S39 (abstract)

Diajil AR, Goodson ML, Thomson PJ (2014). Time to treat: treatment time does not adversely affect clinical outcome following laser excision of oral potentially malignant disorders. *Journal of Oral and Maxillofacial Surgery* Photon 117: 169-178.

https://sites.google.com/site/photonfoundationorganization/home/the-journal-of-oral-and-maxillofacial-surgery

Diajil AR, Robinson CM, Sloan P, Thomson PJ (2013). Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* Article ID 809248, 8 pages http://dx.doi.org/10.1155/2013/809248

Dionne KR, Warnakulasuriya S, Zain RB, Cheong SC (2015). Potentially malignant disorders of the oral cavity: current practice and future directions in the clinic and laboratory. *International Journal of Cancer* 136 : 503-515.

Diz P, Gorsky M, Johnson NW, Kragelund C, Manfredi M, Odell E, Thongprasom K, Warnakulasuriya S, Bagan JV, van der Waal I (2015). Oral leukoplakia and erythroplakia: a protocol for diagnosis and management. European Association of Oral Medicine. http://www.kcl.ac.uk/dentistry/about/acad/oral-leukoplakia-and-erythroplakia.pdf

Donadini A, Maffei M, Cavallero A, Pentenero M, Malacarne D, DiNallo E, Truini M, Navone R, Mereu P, Scala M, Santelli A, Gandolfo S, Giaretti W (2010). Oral cancer genesis and progression: DNA near-diploid aneuploidization and endoreduplication by high resolution flow cytometry. *Cell Oncol* 32 : 373-383.

Downer MC, Moles DR, Palmer S, Speight PM (2004). A systematic review of test performance in screening for oral cancer and precancer. *Oral Oncology* 40 : 264-273.

Dost F, LeCao K, Ford PJ, Farah CS (2013). A retrospective analysis of clinical features of oral malignant and potentially malignant disorders with and without oral epithelial dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol* 116 : 725-733.

Dost F, LeCao K, Ford PJ, Ades C, Farah CS (2014). Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 117 : 343-352.

Dwivedi N, Chandra S, Kashyap B, Raj V, Agarwal A (2013). Suprabasal expression of KI-67 as a marker for the severity of oral epithelial dysplasia and oral squamous cell carcinoma. *Contemp Clin Dent* 4 : 7-12.

Edefonti V, Hashibe M, Ambrogi F, Parpinel M, Bravi F, Talamini R, Levi F, Yu G, Morgenstern H, Kelsey K, McClean M, Schantz S, Zhang Z, Chuang S, Boffetta P, LaVecchia C, Decarli A (2011). Nutrient-based dietary patterns and the risk of head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. *Annals of Oncology* doi:10.1093/annonc/mdr548 : 1-11.

Edwards PC (2014). The natural history of oral epithelial dysplasia: perspective on Dost et al (Editorial). *Oral Surg Oral Med Oral Pathol Oral Radiol* 117 : 263-266.

Einhorn J, Wersall J (1967). Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. *Cancer* 20 : 2189-2193.

ENT-UK (2011). Head and Neck Cancer: Multidisciplinary Management Guidelines (4th edition) https://entuk.org/professionals/publications.

Epstein JB, Gorsky M, Fischer D, Gupta A, Epstein M, Elad S (2007). A survey of the current approaches to diagnosis and management of oral premalignant lesions. *J Am Dent Assoc* 138 : 1555-1562.

Esserman LJ, Thompson IM, Reid B (2013). Overdiagnosis and overtreatment in cancer. An opportunity for improvement. *J American Medical Association* 310 : 797-798.

Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ (2015). The management of oral epithelial dysplasia: The Liverpool algorithm. *Oral Oncology* 51 : 883-887.

Ford PJ, Farah CS (2013). Early detection and diagnosis of oral cancer: strategies for improvement. *Journal of Cancer Policy* 1 : e2-e7 http://dx.doi.org/10.1016/j.jcpo.2013.04.002.

Frame JW (1984). Treatment of sublingual keratosis with the CO_2 laser. *British Dental Journal* 156 : 243-246.

Frame JW (1985). Removal of oral soft tissue pathology with the CO_2 laser. *Journal of Oral & Maxillofacial Surgery* 43 : 850-855.

Frame JW, Das Gupta AR, Dalton GA, Rhys Evans PH (1984). Use of the carbon dioxide laser in the management of premalignant lesions of the oral mucosa. *The Journal of Laryngology and Otology* 98 : 1251-1260.

Gale N, Pilch BZ, Sidransky D, Westra WH, Califano J. Epithelial precursor lesions. In: Barnes L, Eveson JW, Reichart P, Sidransky D editors. World Health Organisation Classification of Tumours. Pathology and Genetics. Head and Neck Tumours. 2005 Lyon: IACR Press; pp140-143.

Giaretti W, Maffei M, Pentenero M, Scaruffi P, Donadini A, DiNallo E, Malacarne D, Marino R, Familiari U, Coco S, Tonini GP, Castagnola P, Gandolfo S (2012). Genomic aberrations in normal appearing mucosa fields distal from oral potentially malignant lesions. *Cell Oncol* 35 : 43-52.

Giaretti W, Monteghirfo S, Pentenero M, Gandolfo S, Malacarne D, Castagnola P (2013). Chromosomal instability, DNA index, dysplasia, and subsite in oral premalignancy as intermediate endpoints of risk of cancer. *Cancer Epidemiol Biomarkers Prev* 22 : 1133-1141.

Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, Michie S, Moher D, Wager E (2014). Research: increasing value, reducing waste 5. Reducing waste from incomplete or unusable reports of biomedical research. *The Lancet* 383 : 267-276.

Gomes CC, Gomez RS (2013). Oral leukoplakia: what is achieved by surgical treatment? *Annals of Oral & Maxillofacial Surgery* 1 : 9.

Gomez I, Warnakulasuriya S, Varela-Centelles PI, Lopez-Jornet P, Suarez-Cunqueiro M, Diz-Dios P, Seoane J (2010). Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay? *Oral Diseases* 16 : 333-342.

Goodson ML, Hamadah O, Thomson PJ (2010a). The role of alcohol in oral precancer: observations from a North-East England population. *British Journal of Oral & Maxillofacial Surgery* 48: 507-510.

Goodson ML, Robinson CM, Sloan P, Thomson PJ (2010b). Malignant transformation – how relevant is oral epithelial dysplasia? *British Journal of Oral & Maxillofacial Surgery* 48 Suppl 1 : 519.

Goodson ML, Thomson PJ (2011). Management of oral carcinoma – benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 88-91.

Goodson ML, Thomson PJ (2014). Tissue autofluorescence and the diagnosis and management of oral potentially malignant disorders. *Journal of Oral and Maxillofacial Surgery* Photon 117 : 205-214. ISJN37924853D663527032014

Goodson ML, Kumar A, Thomson PJ (2011). Oral precancer excision is required for definitive diagnosis: incisional vs. excisional biopsies in oral leukoplakia management. *Oral Oncology* 47 S128-129. doi:10.1016/joraloncology.2011.06.414 (abstract).

Goodson ML, Sloan P, Wadehra V, Johnson SJ, Robinson CM, Mowatt AW, Thomson PJ (2014a). Predicting clinical outcome following oral potentially malignant disorder treatment – the role of adjunctive diagnostic techniques. *Journal of Oral and Maxillofacial Surgery* Photon 117 : 215-223. ISJN37924853D658127032014

Goodson ML, Sloan P, Wadehra V, Johnson SJ, Robinson CM, Aubourg G, Thomson PJ (2014b). Orcellex® brush biopsy and liquid-based cytology – assessment of a new diagnostic technique in oral potentially malignant disorder management. *Journal of Oral and Maxillofacial Surgery* Photon 117 : 224-231. ISJN37924853D666928032014

Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ (2015). Oral Precursor Lesions and Malignant Transformation – Who, Where, What and When? *British Journal of Oral & Maxillofacial Surgery* 53 : 831-835.

Goodson ML, Sugden K, Kometa S, Thomson PJ (2012). Complications following interventional laser surgery for oral cancer and precancerous lesions. *British Journal of Oral & Maxillofacial Surgery* 50 : 597-600.

Gouvea AF, Santos Silva AR, Speight PM, Hunter K, Carlos R, Vargas PA, de Almeida OP, Lopes MA (2013). High incidence of DNA ploidy abnormalities and increased Mcm2 expression may predict malignant change in oral proliferative verrucous leukoplakia. *Histopathology* 62 : 551-562.

Graveland AP, Bremmer JF, de Maaker M, Brink A, Cobussen P, Zwart M, Braakhuis BJM, Bloemena E, van der Waal I, Leemans CR, Brakenhoff RH (2013). Molecular screening of oral precancer. *Oral Oncology* 49 : 1129-1135.

Greaney L, Brennan PA, Kerawala C, Cascarini L, Godden D, Coombes D (2014). Why should I follow up my patients with oral lichen planus and lichenoid reactions? *British Journal of Oral & Maxillofacial Surgery* 52 : 291-293.

Green RA (2013). Patient and professional views and experience of oral precancer. *PhD Thesis* Newcastle University

Greenwood M, Thomson PJ, Lowry RJ, Steen IN (2003). Oral cancer: material deprivation, unemployment and risk factor behaviour - an initial study. *International Journal of Oral & Maxillofacial Surgery* 32 : 74-77.

Gupta PC, Hebert JR, Bhonsle RB, Murti PR, Mehta H, Mehta FS (1999). Influence of dietary factors on oral precancerous lesions in a population-based case-control study in Kerala, India. *Cancer* 85 : 1885-1893.

Hamadah O, Goodson ML, Thomson PJ (2010). Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 48 : 503-506.

Hamadah O, Hepburn S, Thomson PJ (2007). Effects of active non-smoking programmes on smoking behaviour in oral precancer patients. *International Journal of Oral and Maxillofacial Surgery* 36 : 706-711.

Hamadah O, Thomson PJ (2009). Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 41:17-25.

Harman NL, Bruce IA, Callery P, Tierney S, Sharif MO, O'Brien K, Williamson PR (2013). MOMENT – Management of otitis media with effusion in cleft palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 14 : 70 doi: 10.1186/1745-6215-14-70.

Hashibe M, Jacob BJ, Thomas G, Ramadas K, Mathew B, Sankaranarayanan R, Zhang ZF (2003). Socioeconomic status, lifestyle factors and oral premalignant lesions. *Oral Oncology* 39 : 664-671.

Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, DalMaso L, Daudt AW, Fabianova E, Wunsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, LaVecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang Z-F, Berthiller J, Boffetta P (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 99 : 777-789.

Hebbale M, Krishnapra R, Bagewad IA, Keluskar V, Kale A, Halli R (2012). Evaluation of mirror image biopsy for incidence of multiple premalignant and malignant lesions in oral cancer. *Journal of Indian Academy of Oral Medicine & Radiology* 24 : 194-199.

Hingorani A D, Shah T, Kumari M, Sofat R, Smeeth L (2010). Translating genomics into improved healthcare. *BMJ* 341 : 1037-1042.

Hogewind WFC, van der Kwast WAM, van der Waal I (1989). Oral leukoplakia, with emphasis on malignant transformation: A follow-up study of 46 patients. *J Cranio-Maxfac Surg* 17 : 128-133.

Holmstrup P, Vedtofte P, Reibel J, Stoltze K (2006). Long term treatment outcome of oral premalignant lesions *Oral Oncology* 42 5 : 461–474.

Holmstrup P, Vedtofte P, Reibel J, Stoltze K (2007). Oral premalignant lesions: is a biopsy reliable? *J Oral Pathol Med* 36 : 262-266.

Holmstrup P (2009). Can we prevent malignancy by treating premalignant lesions? *Oral Oncology* 45 : 549-550.

Ho P-S, Chen P-L, Warnakulasuriya S, Shieh T-Y, Chen Y-K, Huang I-Y (2009). Malignant transformation of oral potentially malignant disorders in males: a retrospective cohort study. *BMC Cancer*. 9 : article 260.

Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ (2013). Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. *British Journal of Oral & Maxillofacial Surgery* 51 : 594-599.

Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, Rajlawat BP, Triantafyllou A, Rogers SN, Lowe D, Shaw RJ (2012). The clinical determinants of malignant transformation in oral epithelial dysplasia. *Oral Oncology* 48 : 969-976.

Hsue SS, Wang W-C, Chen C-H, Lin C-C, Chen Y-K, Lin L-M (2007) Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *J Oral Pathol Med* 36 : 25–29.

Huff KD, Garren KC, Huff MS (2010). A novel, minimally invasive approach to managing mild epithelial dysplasia. *General Dentistry* March/April : 126-129 www.agd.org.

Ishi J, Fujita K, Komori T (2003). Laser surgery as a treatment for oral leukoplakia. *Oral Oncology* 39 : 759-769.

Ishi J, Fujita K, Munemoto S, Komori T (2004). Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. *J Clin Laser Med Surg* 22 : 27-33.

Issrani R, Prabhu N, Keluskar V (2013). Oral proliferative verrucous leukoplakia: a case report with an update. *Contemp Clin Dent* 4: 258-262.

Jaber MA (2010). Oral epithelial dysplasia in non-users of tobacco and alcohol: an analysis of clinicopathological characteristics and treatment outcome. *J Oral Science* 52 : 13-21.

Jaber MA, Porter SR, Speight P, Eveson JW, Scully C (2003). Oral epithelial dysplasia: clinical characteristics of western European residents. *Oral Oncology* 39 : 589-596.

Jerjes W, Upile T, Hamdoon Z, Al-Khawalde M, Morcos M, Mosse CA, Hopper C (2012a). CO_2 laser of oral dysplasia: clinicopathological features of recurrence and malignant transformation. *Lasers Med Sci* 27 : 169-179.

Jerjes W, Hamdoon Z, Hopper C (2012b). CO_2 lasers in the management of potentially malignant and malignant oral disorders. *Head & Neck Oncology* 4 : 17-22.

Johnson S, McDonald JT, Corsten M, Rourke R (2010). Socio-economic status and head and neck cancer incidence in Canada: a case control study. *Oral Oncology* 46 : 200-203.

Kalavrezos N, Bhandari R (2010). Current trends and future perspectives in the surgical management of oral cancer. *Oral Oncology* 46 : 429-432.

Kanatas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN (2011). The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association of Oral and Maxillofacial Surgeons. *British Journal of Oral & Maxillofacial Surgery* 49 : 99-105.

Koo K, Barrowman R, McCullough M, Iseli T, Wiesenfeld (2013). Non-smoking non-drinking elderly females: a clinically distinct subgroup of oral squamous cell carcinoma patients. *International Journal of Oral & Maxillofacial Surgery* 42 : 929-933.

Krutchkoff DJ, Eisenberg E (1985). Lichenoid dysplasia: a distinct histopathologic entity. *Oral Surg Oral Med Oral Pathol* 60 : 308-315.
Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P (2006). Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. *Oral Oncology* 42 : 987-993.

Kumar A, Cascarini L, McCaul JA, Kerawala CJ, Coombes D, Godden D, Brennan PA (2013). How should we manage oral leukoplakia? *British Journal of Oral & Maxillofacial Surgery* 51 : 377-383.

Lagiou P, Georgila C, Minaki P, Ahrens W, Pohlabeln H, Benhamou S, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane TV, Macfarlane GJ, Talamini R, Barzan L, Canova C, Simonato L, Lowry RJ, Conway DI, McKinney PA, Znaor A, McCartan BE, Healy C, Nelis M, Metspalu A, Marron M, Hashibe M, Brennan PJ (2009a). Alcohol-related cancers and genetic susceptibility in Europe: the ARCAGE project: study samples and data collection. *Eur J Cancer Prev* 18 : 76-84.

Lagiou P, Talamini R, Samoli E, Lagiou A, Ahrens W, Pohlabeln H, Benhamou S, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane TV, Macfarlane GJ, Biggs A-M, Barzan L, Canova C, Simonato L, Lowry RJ, Conway DI, McKinney PA, Znaor, McCartan BE, Healy CM, Marron M, Hashibe M, Brennan P (2009b). Diet and upper-aerodigestive tract cancer in Europe: the ARCAGE study. *Int J Cancer* 124 : 2671-2676.

Lee J-J, Hong WK, Hittelman WN, Mao L, Lotan R, Shin DM, Benner SE, Xu X-C, Lee JS, Papadimitrakopoulou, Geyer C, Perez C, Martin JW, El-Naggar AK, Lippman SM (2000). Predicting cancer development in oral leukoplakia: ten years of translational research. *Clinical Cancer Research* 6 : 1702-1710.

Lee J-J, Hung H-C, Cheng S-J, Chiang C-P, Liu B-Y, Yu C-H, Jeng J-H, Chang H-H, Kok S-H (2007). Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104 : 217-225.

Lee Y-C, Zugna D, Richiardi L, Merletti F, Marron M, Ahrens W, Pohlabeln H, Lagiou P, Trichopoulos D, Agudo A, Castellsague X, Betka J, Holcatova I, Kjaerheim K, Macfarlane GJ, Macfarlane TV, Talamini R, Barzan L, Canova C, Simonato L, Conway DI, McKinney PA, Thomson PJ, Znaor A, Healy CM, McCartan BE, Boffetta P, Brennan P, Hashibe M (2013). Smoking addiction and the risk of upper-aerodigestive-tract cancer in a multicenter case-control study. *International Journal of Cancer* 133 : 2688-2695.

Leoncini E, Ricciardi W, Cadoni G, Arzani D, Petrelli L, Paludetti G, Brennan P, Luce D, Stucker I, Matsuo K, Talamini R, LaVecchia C, Olshan A, Winn D, Herrero R, Franceschi S, Castellsague X, Muscat J, Morgenstern H, Zhang Z-F, Levi F, DalMaso L, Kelsey K, McClean M, Vaughn T, Lazarus P, Purdue M, Hayes R, Chen C, Schwartz S, Shangina O, Koifgman S, Ahrens W, Matos E, Lagiou P, Lissowska J, Fernandez L, Menezes A, Agudo A, Simonato L, Brener H, Conway D, Macfarlane T, Thomson PJ, Znaor A, Rudnai P, Healy C, Boffetta P, Hashibe M, Boccia S (2014). Adult height and head and neck cancer: a pooled analysis within the INHANCE consortium. *European Journal of Epidemiology* 29 : 35-48.

Leston JS, Dios PD (2010). Diagnostic clinical aids in oral cancer. *Oral Oncology* 46 : 418-422.

Lian I-B, Tseng Y-T, Su C-C, Tsai K-Y (2013). Progression of precancerous lesions to oral cancer: results based on the Taiwan National Health Insurance Database. *Oral Oncology* 49 : 427-430.

Lim B, Smith A, Chandu A (2010). Treatment of oral leukoplakia with carbon dioxide and potassium-titanyl-phosphate lasers: a comparison. *J Oral Maxillofac Surg* 68 : 597-601.

Lingen MW, Kalmar JR, Karrison T, Speight PM (2008). Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncology* 44 : 10-22.

Liu S-C, Sauter ER, Clapper ML, Feldman RS, Levin L, Chen S-Y, Yen TJ, Ross E, Engstrom PF, Klein-Szanto AJP (1998). Markers of cell proliferation in normal epithelia and dysplastic leukoplakias of the oral cavity. *Cancer Epidemiology, Biomarkers & Prevention* 7 : 597-603.

Liu W, Bao Z-X, Shi L-J, Tang G-Y, Zhou Z-T (2011). Malignant transformation of oral epithelial dysplasia: clinicopathological risk factors and outcome analysis in a retrospective cohort of 138 cases. *Histopathology* 59 : 733-740.

Lodi G, Porter S (2008). Management of potentially malignant disorders: evidence and critique. *J Oral Pathol Med* 37 : 63-69.

Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A (2006). Interventions for treating oral leukoplakia. *Cochrane Database of Systematic Reviews* Issue 4. DOI: 10.1002/14651858.CD001829.pub3.

Lovas JG, Harsanyi BB, ElGeneidy AK (1989). Oral lichenoid dysplasia: a clinicopathologic analysis. *Oral Surg Oral Med Oral Pathol* 68 : 57-63.

Lumerman H, Freedman P, Kerpel S (1995). Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol* 79 : 321-329.

Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C (2015). Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. *Cochrane Database Syst Rev* 5 : CD010276. DOI:10.1002/14651858.CD01026.pub2.

Macfarlane TV, Macfarlane GJ, Oliver RJ, Benhamou S, Bouchardy C, Ahrens W, Pohlabeln H, Lagiou P, Lagiou A, Castellsagu X, Agudo A, Merletti F, Richiardi L, Kjaerheim K, Slamova A, Schejbalova M, Canova C, Simonato L, Talamini R, Barzan L, Conway DI, McKinney PA, Znaor A, Lowry RJ, Thomson PJ, Healy CM, McCartan BE, Marron M, Hashibe M, Brennan P (2010). The aetiology of upper aerodigestive tract cancers among young adults in Europe: The ARCAGE study. *Cancer Causes Control* 21 : 2213-2221.

Macfarlane T, Macfarlane G, Thakker N, Benhamou S, Bouchardy C, Ahrens W, Pohlabeln H, Lagiou P, Lagiou A, Castellsague X, Agudo A, Slamova A, Pizak J, Merletti F, Richiardi L, Talamini R, Barzan L, Kjaerheim K, Canova C, Simonato L, Conway D, McKinney P, Thomson PJ, Sloan P, Znaor A, Healy C, McCartan B, Marron M, Brennan P (2012). Role of medical history and medication use in the aetiology of upper aerodigestive tract cancers in Europe: the ARCAGE study. *Annals of Oncology* 4 : 1053-1060.

Mandal S, Agrawal R, Salgotra V, Kohli S (2014). Management of potentially malignant disorders of oral cavity: role of medical therapies. *International Journal of Dental and Health Sciences* 1 : 187-193.

Marley JJ, Cowan CG, LameyP-J, Linden GJ, Johnson NW, Warnakulasuriya KAAS (1996). Management of potentially malignant oral mucosal lesions by consultant UK oral and maxillofacial surgeons. *British Journal of Oral & Maxillofacial Surgery* 34 : 28-36.

Marley JJ, Linden GJ, Cowan CG, Lamey P-J, Johnson NW, Warnakulasuriya KAAS, Scully C (1998). A comparison of the management of potentially malignant oral mucosal lesions by oral medicine practitioners and oral & maxillofacial surgeons in the UK. *J Oral Pathol Med* 27 : 489-495.

Marron M, Boffetta P, Moller H, Ahrens W, Pohlabeln H, Benhamou S, Bouchardy C, Lagiou P, Lagiou A, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane T, Macfarlane G, Talamini R, Barzan L, Canova C, Simonato L, Biggs A-M, Thomson PJ, Conway D, McKinney P, Znaor A, Healy C, McCartan B, Brennan P, Hashibe M (2012). Risk of upper aerodigestive tract cancer and type of alcoholic beverage: a European multicentre case-control study. *European Journal of Epidemiology* 27: 499-517.

Marorell-Calatayud A, Botella-Estrada R, Bagan-Sebastian JV, Sanmartin-Jimenez O (2009). Oral leukoplakia: clinical, histopathologic, and molecular features and therapeutic approach. *Actas Dermosifilogr* 100 : 669-684.

Matsumoto K, Suzuki H, Asai T, Wakabayashi R, Enomoto Y, Kitayama M, Shigeoka M, Kimoto A, Takeuchi J, Yutori H, Komori T (2015). Clinical investigation of carbon dioxide laser treatment for lingual leucoplakia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 27 : 493-497.

McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D (2002). Randomised trials in surgery: problems and possible solutions. *British Medical Journal* 324 : 1448-1451.

McKie C, Ahmad UA, Fellows S, Meikle D, Stafford FW, Thomson PJ, Welch AR, Paleri V (2008). The 2-week rule for suspected head and neck cancer in the United Kingdom: Referral patterns, diagnostic efficacy of the guidelines and compliance. *Oral Oncology* 44 : 851-856.

Messadi DV (2013). Diagnostic aids for detection of oral precancerous conditions. *International Journal of Oral Science* 5 : 59-65.

Mehanna HM, Rattay T, Smith J, McConkey CC (2009). Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 31 : 1600-1609.

Mehanna H, Paleri V, West CML, Nutting C (2010a). Head and neck cancer – Part 1: Epidemiology, presentation, and prevention. *Br Medical Journal* 341 : 663-666.

Mehanna H, West CML, Nutting C, Paleri V (2010b). Head and neck cancer – Part 2: Treatment and prognostic factors. *Br Medical Journal* 341 : 721-725.

Mignogna MD, Fedele S, LoRusso L, Mignogna C, de Rosa G, Porter SR (2007). Field cancerization in oral lichen planus. *EJSO* 33 : 383-389.

Mishra R (2012). Biomarkers of oral premalignant epithelial lesions for clinical application. *Oral Oncology* 48 : 578-584.

Mishra R (2013). Cell cycle-regulatory cyclins and their deregulation in oral cancer. *Oral Oncology* 49 : 475-481.

Mogedas-Vegara A, Hueto-Madrid J-A, Chimenos-Kustner E, Bescos-Atin C (2015). The treatment of oral leukoplakia with the CO_2 laser: a retrospective study of 65 patients. *Journal of Cranio-Maxillo-Facial Surgery* 43 : 677-681.

Moles DR, Downer MC, Speight PM (2002). Meta-analysis of measures of performance reported in oral cancer and precancer screening studies. *British Dental Journal* 192 : 340-344.

Mortazavi H, Baharvand M, Mehdipour M (2014). Oral potentially malignant disorders: an overview of more than 20 entities. *Journal of Dental Research, Dental Clinics, Dental Prospects* 8 : 6-14.

Mullin MH, Brierley DJ, Speight PM (2015). Second opinion reporting in head and neck pathology: the pattern of referrals and impact on final diagnosis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 119 : 656-660.

Nankivell P, Mehanna H (2011). Oral dysplasia: biomarkers, treatment and follow-up. *Curr Oncol Rep* 13 : 145-152.

Nankivell P, Dunn J, Langman M, Mehanna H (2012). Feasibility of recruitment to an oral dysplasia trial in the United Kingdom. *Head & Neck Oncology* 4 : 40.

Napier SS, Speight PM (2008). Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med* 37 : 1-10.

National Cancer Intelligence Network (2014). Head and Neck Cancer Profiles *www.ncin.org.uk*

Office for National Statistics (2012). Census gives insights into characteristics of the North East's population. *www.ons.gov.uk/census*

O'Hanlon S, Forster DP, Lowry RJ (1997). Oral cancer in the North-East of England: incidence, mortality trends and the link with material deprivation. *Community Dent Oral Epidemiol* 25 : 371-376.

Pandis N (2013). Randomized clinical trials (RCTs) and systematic reviews (SRs) in the context of evidence-based orthodontics (EBO). *Seminars in Orthodontics* 19 : 142-157.

Papadimitrakopoulou VA, William WN, Dannenberg AJ, Lippman SM, Lee JJ, Ondrey FG, Peterson DE, Feng L, Atwell A, El-Naggar AK, Nathan C-A, Helman JI, Du B, Yueh B, Boyle JO (2008). Pilot randomized phase II study of celecoxib in oral premalignant lesions. *Clinical Cancer Research* 14 : 2095-2101.

Patil S, Rao R, Sanketh S, Warnakulasuriya S (2014). Lichenoid dysplasia revisited – evidence from a review of Indian archives. *J Oral Pathol Med* 44 : 507-514.

Pentenero M, Carrozzo M, Pagano M, Galliano D, Broccoletti R, Scully C, Gandolfo S (2003). Oral mucosal dysplastic lesions and early squamous cell carcinomas: underdiagnosis from incisional biopsy. *Oral Diseases* 9 : 68-72.

Pentenero M, Giaretti W, Navone R, Demurtas A, Rostan I, Bertolusso G, Broccoletti R, Arduino PG, Malacarne D, Gandolfo S (2009). DNA aneuploidy and dysplasia in oral potentially malignant disorders: association with cigarette smoking and site. *Oral Oncology* 45 : 887-890.

Pentenero M, Donadini A, DiNallo E, Maffei M, Marino R, Familiari U, Castagnola P, Gandolfo S, Giaretti W (2012). Field effect in oral precancer as assessed by DNA flow cytometry and array-CGH. *J Oral Pathol Med* 41 : 119-123.

Petti S (2003). Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncology* 39 : 770-780.

Petti S (2009). Lifestyle risk factors for oral cancer. *Oral Oncology* 45 : 340-350.

Poate TW, Warnakulasuriya S (2006). Effective management of smoking in an oral dysplasia clinic in London. *Oral Diseases* 12 : 22-26.

Potter S, Mills N, Cawthorn SJ, Donovan J, Blazeby JM (2014). Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomized clinical trials in surgery? A qualitative study. *Trials* 15 : 80 doi:10.1186/1745-6215-15-80.

Price G, Roche M, Wight R (2014). The impact of head and neck cancer service guidance on surgical workload. *Annals of the Royal College of Surgeons of England (Supplement)* 96 : 300-303.

Public Health England (2015). Newcastle upon Tyne. *www.healthprofiles.info*

Pulino BdeFB, dos Santos JFM, Pastore GP, Radaic P, Filho GPdeC, Pereira RA (2011). Oral cancer: potentially malignant lesions and statistics of diagnosed cases in the municipality of Santo Andre-SP. *J Health Sci Inst* 29 : 231-234.

Rastogi V, Puri N, Mishras S, Arora S, Kaur G, Yadav L (2013). An insight to oral epithelial dysplasia. *Int J Head & Neck Surg* 4 : 74-82.

Rautava J, Luukkaa M, Heikinheimo K, Alin J, Grenman R, Happonen R-P (2007). Squamous cell carcinomas arising from different types of oral epithelia differ in their tumor and patient characteristics and survival. *Oral Oncology* 43 : 911-919.

Reibel J (2003). Prognosis of oral pre-malignant lesions: significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med* 14 : 47-62.

Reichart PA (2001). Identification of risk groups for oral precancer and cancer and preventive measures. *Clin Oral Invest* 5 : 207-213.

Ribeiro AS, Salles PR, daSilva TA, Mesquita RA (2010). A review of the nonsurgical treatment of oral leukoplakia. *International Journal of Dentistry* 2010 doi:10.1155/2010/186018.

Ribeiro FAP, Noguti J, Oshima CTF, Ribeiro DA (2014). Effective targeting of the epidermal growth factor receptor (EGFR) for treating oral cancer: a promising approach. *Anticancer Research* 34 : 1547-1552.

Richiardi M, Corbin M, Marron M, Ahrens W, Pohlabein H, Lagiou P, Minaki P, Agudo A, Castellsague X, Slamova A, Schejbalova M, Kjaerhiem K, Barzan L, Talamini R, Macfarlane GJ, Macfarlane T, Canova C, Simonato L, Conway DI, McKinney P, Sneddon L, Thomson PJ, Znoar A, Healy C, McCartan B, Benhamou S, Bouchardy C, Hashibe M, Brennan P, Merletti F (2012). Occupation and risk of upper aerodigestive tract cancer: The ARCAGE study. *International Journal of Cancer* 130 : 2397-2406.

Rogers SN, Ahad SA, Murphy AP (2007). A structured review and theme analysis of papers published on 'quality of life' in head and neck cancer: 2000-2005. *Oral Oncology* 43 : 843-868.

Roodenburg JLN, Panders AK, Vermey A (1991). Carbon dioxide laser surgery of oral leukoplakia. *Oral Surg Oral Med Oral Pathol* 71 : 670-674.

Saito T, Suguira C, Hirai A, Notani K, Totsuka Y, Shindoh M, Fukuda H (2001). Development of squamous cell carcinoma from pre-existent oral leukoplakia: with respect to treatment modality. *International Journal of Oral & Maxillofacial Surgery* 30 : 49-53.

Sarode SC, Sarode GS, Karmarkar S, Tupkari JV (2011). A new classification for potentially malignant disorders of the oral cavity. *Oral Oncology* 47 : 920-921.

Schaaij-Visser TB, Bremmer JF, Braakhuis BJ, Heck AJ, Slijper M, van der Waal I, Brakenhoff RH (2010). Evaluation of cornulin, keratin 4, keratin 13 expression and grade of dysplasia for predicting malignant progression of oral leukoplakia. *Oral Oncology* 46 : 123-127.

Schepman KP, van der Meij EH, Smeele LE, van der Waal I (1998). Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncology* 34 : 270-275.

Scott SE, Grunfeld EA, Auyeung V, McGurk M (2009). Barriers and triggers to seeking help for potentially malignant oral symptoms: implications for interventions. *Journal of Public Health Dentistry* 69 : 34-40.

Scully C, Petti S (2010). Overview of cancer for the healthcare team: aetiopathogenesis and early diagnosis. *Oral Oncology* 46 : 402-406.

Seoane J, Caballero TG, Urizar JMA, Almagro M, Mosquera AG, Varela-Centelles P (2010). Pseudodysplastic epithelial artefacts associated with oral mucosa CO_2 laser excision: an assessment of margin status. *International Journal of Oral & Maxillofacial Surgery* 39 : 783-787.

daSilva SD, Ferlito A, Takes RP, Brakenhoff RH, Valentin MD, Woolgar JA, Bradford CR, Rodrigo JP, Rinaldo A, Hier MP, Kowalski LP (2011). Advances and applications of oral cancer basic research. *Oral Oncology* 47 : 783-791.

Shah JP, Gil Z (2009). Current concepts in management of oral cancer – Surgery. *Oral Oncology* 45 : 394-401.

Shani T, Onn A, Kabha A, Ben-Dov I, Adam I, Amariglio N, Yahalom R, Rechavi G, Trakhtenbrot L, Hirshberg A (2010). Chromosomal numerical aberrations in apparently normal oral mucosa of heavy smokers affected by lung cancer. *Oral Oncology* 46 : 96-99.

Shirani S, Kargahi N, Razavi SM, Homayoni S (2014). Epithelial dysplasia in oral cavity. *Iranian Journal of Medical Science* 39 : 406-417.

Shiu MN, Chen TH (2003). Intervention efficacy and malignant transformation to oral cancer among patients with leukoplakia. *Oncol Report* 10 : 1683-1692.

Siar CH, Mah MC, Gill PP, Nagatsuka H, Tsujigiwa H, Gunduz M, Nagai N, Ng KH (2005). Oral potentially malignant epithelial lesions and associated risk in the contralateral mucosa. *J Hard Tissue Biology* 14 : 183-184.

Silverman S, Gorsky M, Lozada F (1984). Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer* 53: 563-568.

Sitheeque MAM, Samaranayake LP (2003). Chronic hyperplastic candidosis / candidiasis (candida leukoplakia). *Crit Rev Oral Biol Med* 14 : 253-267.

Slaughter DP, Southwick HW, Smejkal W (1953). Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. *Cancer* 6 : 963-968.

Sloan P (2012). Pathological aspects of oral precancer. In P J Thomson (Ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders.* Wiley-Blackwell 2012 : 93-106 ISBN 978-1-4443-3574-3

Smith J, Rattay T, McConkey C, Helliwell T, Mehanna H (2009). Biomarkers in dysplasia of the oral cavity: a systematic review. *Oral Oncology* 45 : 647-653.

Soares CP, Zuanon JAS, Teresa DB, Fregonezi PA, Neto CB, Oliveira MRB, Donadi EA, Martinelli-Klay CP, Soares EG (2006). Quantitative cell-cycle protein expression in oral cancer assessed by computer-assisted system. *Histology & Histopathology* 21 : 721-728.

Solutions for Public Health (2015). Appraisal of Screening for Oral Cancer. A draft report for the UK National Screening Committee. www.sph.nhs.uk

Speight PM (2007). Update on oral epithelial dysplasia and progression to cancer. *Head and Neck Pathol* 1 : 61-66.

Speight PM, Torres-Rendon A (2011). Oral epithelial dysplasia may progress to squamous cell carcinoma. *Pathology Case Reviews* 16 : 141-144.

Speight PM, Abram TJ, Floriano PN, James R, Vick J, Thornhill MH, Murdoch C, Freeman C, Hegarty AM, D'Apice K, Kerr AR, Phelan J, Corby P, Khouly I, Vigneswaran N, Bouquot J, Demian NM, Weinstock YE, Redding SW, Rowan S, Yeh CK, McGuff HS, Miller FR, McDevitt JT (2015). Interobserver agreement in dysplasia grading: towards an enhanced gold standard for clinical pathology trials. *Oral Surg Oral Med Oral Pathol Oral Radiol* 120 : 474-482.

Sperandio M, Brown AL, Lock C, Morgan PR, Coupland VH, Madden PB, Warnakulasuriya S, Moller H, Odell EW (2013). Predictive value of dysplasia grading and DNA ploidy in malignant transformation of oral potentially malignant disorders. *Cancer Prev Res* 8 : 822-831.

Stocker J, Thomson PJ, Hamadah O (2005). Laser surgery in oral oncology – the Newcastle experience. *The Surgeon* 3 S32-33 (abstract).

Syrjanen S, von Bultzingslowen I, Aliko A, Arduino P, Campisi G, Challacome S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M (2011). Human papillomavirus in oral carcinoma and oral potentially malignant disorders: a systematic review. *Oral Diseases* 17 (Suppl 1) : 58-72.

Tadakamadla J, Kumar S, Johnson NW (2015). Quality of life in patients with oral potentially malignant disorders: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 119 : 644-655.

Thomson PJ (2002). Field change and oral cancer: new evidence for widespread carcinogenesis. *International Journal of Oral & Maxillofacial Surgery* 31:262-266.

Thomson PJ (2012a). Introduction. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders.* Wiley-Blackwell : 1-12 ISBN 978-1-4443-3574-3

Thomson PJ (2012b). Oral Carcinogenesis. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders.* Wiley-Blackwell : 31-47 ISBN 978-1-4443-3574-3

Thomson PJ (2012c). Management of Oral Precancer. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 107-137 ISBN 978-1-4443-3574-3

Thomson PJ (2012d). Clinical Outcome. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 138-155 ISBN 978-1-4443-3574-3

Thomson PJ (2012e). Malignant Transformation and Oral Cancer Development. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 156-169 ISBN 978-1-4443-3574-3

Thomson PJ (2012f). Science, surgery, and surveillance: stopping the clock in oral cancer. *Research Report 2010-2012, Royal College of Surgeons of Edinburgh* 96-99.

Thomson PJ (2014). The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 5: 84-89.

Thomson PJ (2015). Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 6 : 186-191.

Thomson PJ, Goodson ML (2012a). Clinical Presentation of Oral Precancer. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 48-74 ISBN 978-1-4443-3574-3

Thomson PJ Goodson ML (2012b). Diagnostic Methods. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 75-92 ISBN 978-1-4443-3574-3

Thomson PJ, Goodson ML (2012c). The Future. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell : 170185 ISBN 978-1-4443-3574-3

Thomson PJ, Goodson ML (2015). Transoral Laser Microsurgery of the Oral Cavity. In: M Bernal-Sprekelsen, I Vilaseca (ed) Transoral Laser Microsurgery of Benign and Malignant Lesions. Thieme : 124-130 ISBN 978-3-13-172391-8.

Thomson PJ, Goodson ML, Booth C, Cragg N, Hamadah O (2008). Predicting recurrence after treatment of oral precancer: Use of cell cycle analysis. *British Journal of Oral and Maxillofacial Surgery* 46 : 370-375.

Thomson PJ, Goodson ML, Hamadah O (2009). Cohort studies in oral precancer management: intervention vs. observation. *Oral Oncology* Supplement 3 : 116 doi:10.1016/j.oos.2009.06.266 (abstract).

Thomson PJ, Goodson ML, Diajil A, Sloan P (2010). Tissue autofluorescence – an aid to excision margins in oral precancer surgery. *British Journal of Oral & Maxillofacial Surgery* 48 Suppl 1 : 527.

Thomson PJ, Hamadah O (2007). Cancerisation within the oral cavity. The use of 'field mapping biopsies' in clinical management. *Oral Oncology* 43 : 20-26.

Thomson PJ, Hamadah O, Goodson ML, Booth C, Cragg N (2006). Cyclin A predicts clinical outcome in oral precancer and cancer. *International Journal of Oral & Maxillofacial Surgery* 35:1041-1046.

Thomson PJ, McCaul JA, Ridout F, Hutchison IL (2015). To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. *British Journal of Oral & Maxillofacial Surgery* 53 : 1027-1031.

Thomson PJ, Potten CS, Appleton DR (1999a). Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis? *British Journal of Oral & Maxillofacial Surgery* 37:377-383.

Thomson PJ, Potten CS, Appleton DR (1999b). Characterization of epithelial cell activity in patients with oral cancer. *British Journal of Oral & Maxillofacial Surgery* 37:384-390.

Thomson PJ, Potten CS, Appleton DR (2001). In-vitro labelling studies and the measurement of epithelial cell proliferative activity in the human oral cavity. *Archives of Oral Biology* 46:1157-1164.

Thomson PJ, Soames JV, Potten CS, Booth C (2002). Epithelial cell proliferative activity and oral cancer progression. *Cell Proliferation* 35(Suppl.1):110-120.

Thomson PJ, Wylie J (2002). Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 31:145-153.

Tilakaratne WM, Sherriff M, Morgan PR, Odell EW (2011). Grading oral epithelial dysplasia: analysis of individual features. *J Oral Pathol Med* 40 : 533-540.

Torres-Rendon A, Stewart R, Craig GT, Wells M, Speight PM (2009). DNA ploidy analysis by image cytometry helps to identify oral epithelial dysplasias with a high risk of malignant progression. *Oral Oncology* 45 : 468-473.

Tuffin JR, Carruth JAS (1980). The carbon dioxide surgical laser. *British Dental Journal* 156 : 243-246.

van der Hem PS, Nauta JMK, van der Wal JE, Roodenburg JL (2005). The results of CO_2 laser surgery in patients with oral leukoplakia: a 25 year follow up. *Oral Oncology* 41 : 31-37.

van der Meij EH, Mast H, van der Waal I (2007). The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. *Oral Oncology* 43 : 742-748.

van der Waal I (2009a). Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 45 : 317-323.

van der Waal I (2009b). Oral lichen planus and oral lichenoid lesions: a critical appraisal with emphasis on the diagnostic aspects. *Med Oral Patol Oral Cir Buccal* 14 : e310-314.

van der Waal I (2010). Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncology* 46 : 423-425.

van der Waal I (2014). Oral potentially malignant disorders: is malignant transformation predictable and preventable? *Med Oral Patol Oral Cir Bucal* 19 : e386-390.

van der Waal I, Reichart PA (2008). Oral proliferative verrucous leukoplakia revisited. *Oral Oncology* 44 : 719-721.

Villa A, Gohel A (2014). Oral potentially malignant disorders in a large dental population. *J Appl Oral Science* 22 : 473-476.

Vladimirov BS, Schiodt M (2009). The effect of quitting smoking on the risk of unfavorable events after surgical treatment of oral potentially malignant lesions. *Int J Oral Maxfac Surg* 38 : 1188-1193.

Walsh T, Liu JLY, Brocklehurst P, Glenny A-M, Lingen M, Kerr AR, Ogden G, Warnakulasuriya S, Scully C (2013). Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database of Systematic Reviews* Issue 11. DOI: 10.1002/14651858.CD010173.pub2.

Wan Y, Liang F, Nakasone T, Sunakawa H (2014). Development of new leukoplakias and leukoplakia-associated second/multiple primary oral cancers: A case report and literature review. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 26 : 166-169.

Warnakulasuriya S (2001). Histological grading of oral epithelial dysplasia: revisited. *J Pathol* 194 : 294-297.

Warnakulasuriya S (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology* 45 : 309-316.

Warnakulasuriya S (2010). Causes of oral cancer – an appraisal of controversies. *Br Dental Journal* 207 : 471-475.

Warnakulasuriya S, Ariyawardana A (2015). Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med* doi: 10.1111/jop.12339.

Warnakulasuriya S, Johnson NW, van der Waal I (2007). Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 36 : 575-580.

Warnakulasuriya S, Dietrich T, Bornstein MM, Casals Peidro E, Preshaw PM, Walter C, Wennstrom JL, Bergstrom J (2010). Oral health risks of tobacco use and effects of cessation. *International Dental Journal* 60 : 7-30.

Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, Moller H (2011). Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. *J Oral Pathol Med* 40 : 677-683.

Warnakulasuriya S, Fennell N, Seoane J, Rapidis A (2015). An appraisal of oral cancer and pre-cancer screening programmes in Europe: a systematic review. *J Oral Pathol Med* 44 : 559-570.

Watabe Y, Nomura T, Onda T, Yakushiji T, Yamamoto N, Ohata H, Takano N, Shibahara T (2015). Malignant transformation of oral leukoplakia with a focus on low-grade dysplasia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* http://dx.doi.org/10.1016/j.ajoms.2015.02.007.

Werner JA, Dunne AA, Folz BJ, Lippert BM (2002). Transoral laser microsurgery in carcinomas of the oral cavity, pharynx and larynx. *Cancer Control* 9 : 379-386.

Williams M, Bethea J (2011). Patient awareness of oral cancer health advice in a dental access centre: a mixed methods study. *British Dental Journal* 210 : E9.

World Health Organisation (2010). ICD-10 Second Edition Volume 2. www.icd10data.com.

Xue JL, Fan MW, Wang SZ, Chen XM, Li Y, Wang L (2005). A clinical study of 674 patients with oral lichen planus in China. *J Oral Pathol Med* 34 : 467–72.

Yang SW, Tsai CN, Lee YS, Chen TA (2011). Treatment outcome of dysplastic leucoplakia with carbon dioxide laser – emphasis on the factors affecting recurrence. *J Oral Maxillofac Surg* 69 : 78-87.

Yardimci G, Kutlubay Z, Engin B, Tuzun Y (2014). Precancerous lesions of oral mucosa. *World Journal of Clinical Cases* 16 : 866-872.

Ye Y, Lippman SM, Lee JJ, Chen M, Frazier ML, Spitz MR, Wu X (2008). Genetic variations in cell-cycle pathway and the risk of oral premalignant lesions. *Cancer* 113 : 2488-2495.

Zain RB (2001). Cultural and dietary risk factors of oral cancer and precancer – a brief overview. *Oral Oncology* 37 : 205-210.

Zhang L, Cheung KJ, Lam WL, Cheng X, Poh C, Priddy R, Epstein J, Le ND, Rosin MP (2001). Increased genetic damage in oral leukoplakia from high risk sites: potential impact on staging and clinical management. *Cancer* 91 : 2148-2155.

APPENDIX I:

Caldicott Approval for PMD Database

(NUTH NHS Foundation Trust 2015)

APPENDIX II:

Newcastle PMD Patient Demographic Database

(2015)

APPENDIX III:

Newcastle PMD Clinic Data

(Unpublished Audit 2008)

APPENDIX IV:

Interventional Laser Surgery Database

(2015)

APPENDIX V:

Clinico-Pathological PMD Database

(1996-2014)